SCIENTIFIC DISCUSSION

1 Introduction

Non-small-cell lung cancer

Lung cancer is the most frequent or second most frequent type of cancer among European men and ranks third or higher among European women. Prognosis is poor with relative 1-year survival rates of approximately 30% and 5-year survival rates around 10%. 134.171 men and 29.948 women died of lung cancer in the European Union in 1985 [1]. Although the standardised mortality ratio is declining slightly in men it is still rising in women in the vast majority of European Countries [2].

Non-small-cell lung cancer (NSCLC) accounts for approximately 75% of lung cancers. Surgery is the preferred treatment of patients with early disease but more than 60-65% of patients present with locally advanced (stage IIIB) or metastatic disease (stage IV) and are not suitable for surgery. Virtually no patient with a disease staged as IIIB or IV will survive and the primary goal of therapy is palliative. However, moderate gains in survival and other important outcomes like time to disease progression and quality of life have been shown with platinum-based chemotherapy [3, 4]. The current standard of first-line treatment in patients with advanced disease consists of a two-drug platinum-based chemotherapy where 1-year survival rates of 33% and 2-year survival rates of 11% have been reported [5]. Initial therapy will ultimately fail and second-line chemotherapy therapy might be considered.

Practices have varied as to second-line chemotherapy for NSCLC, and until recently the benefits of second-line chemotherapy had not been well established and were mainly based phase II trials [6]. More recently, one phase III trial comparing docetaxel to best supportive care has established a positive benefit risk profile of docetaxel 75 mg/m2 in second line treatment of NSCLC, with positive effects on survival, progression-free survival, and reduced need for symptomatic treatment and radiotherapy [7, 8]. Pemetrexed has also been authorised as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy [9, 10].

Patients progressing after possible second-line therapy with docetaxel are usually treated with best supportive care and palliative radiation. Gefitinib, a HER1/EGFR-tyrosine kinase inhibitor of the same class as erlotinib, has been approved in some countries as third-line therapy based on phase II trials despite unknown benefits compared to best supportive care.

About the product

EGFR is a trans-membrane glycoprotein consisting of a single polypeptide chain. EGFR belongs to a family of structurally related receptor tyrosine kinases (TK) that play a critical role in many cell-signalling pathways that influence cell division, apoptosis, motility and adhesion [11]. The binding of a ligand to the EGFR initiates a cascade of events, with signal transduction culminating in nuclear gene activation. EGFR is believed to be important in multiple signal-transduction pathways and appears to play a critical role in both tumorigenesis and tumor growth. EGFR and its ligands are overexpressed or involved in autocrine growth loops in a number of tumor types, including NSCLC [12-14]. An increase in EGFR expression appears to correlate with aggressive morphology and poor outcome in NSCLC [15, 16] and poor response to therapy [17].

Tarceva contains erlotinib (formerly OSI-774, CP-358,74, R 1415, NSC 718781), a quinazoline derivative, which is an inhibitor of EGFR TK. Erlotinib hydrochloride exists as an anhydrous crystalline solid with three known polymorphs (A,B,E), of which modification A is the thermodynamically most stable form that is provided from routine drug processing. Erlotinib hydrochloride is sparingly soluble in organic solvents and water. Erlotinib has no chiral centres. The molecular weight of the hyrdrochloride salt is 429.9.

The program leading to the discovery of erlotinib was initiated in the early 1990s. In vitro testing of erlotinib demonstrated a specific and potent inhibition of EGFR (IC_{50} = 2 nM) [18]. Subsequent in vivo experiments assessed EGFR inhibition in human tumour xenograft efficacy models, bioavailability and pharmacokinetic properties. Phase I studies in healthy subjects and cancer patients assessed the safety and pharmacokinetics of erlotinib at various dose levels, suggesting a fixed daily oral dose of 150 mg as the recommended dose for Phase II studies. In a Phase II study in patients with NSCLC who had progressed despite platinum-based chemotherapy, a 12.3% objective response rate and a median overall survival of 8.4 months were observed [19]. Subsequently, two Phase III trials of

erlotinib in first-line NSCLC with combination chemotherapy, were initiated. In addition, a Phase III study of erlotinib as single agent in patients with NSCLC after failure of at least one prior chemotherapy regimen (Study BR.21) was conducted. In this trial, a significantly longer overall survival and progression-free survival was observed for erlotinib compared to best supportive care [20].

2 Quality aspects

Introduction

The product is presented as film coated tablet containing 25 mg, 100 mg and 150 mg of erlotinib (as erlotinib hydrochloride) as active substance. Other ingredients are lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, magnesium stearate, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycol, titanium dioxide, and printing ink (colorants included).

The tablets are packed in PVC blister sealed with aluminium foil.

Active Substance

Erlotinib hydrochloride is a white to pale yellow crystalline, non-hygroscopic powder and sparingly soluble in organic solvents, water and aqueous buffer with the chemical name N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, monohydrochloride. Erlotinib hydrochloride is an anhydrous crystalline solid with three known polymorphic forms and has a non-chiral molecular structure.

- Manufacture

Erlotinib hydrochloride is synthesised in two steps Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents, have been presented. A reprocessing procedure may be performed.

The polymorphic forms have been characterised. The manufacturing process leads only to one polymorphic form.

Batch analysis data produced with the proposed synthetic route provided show that the active substance can be manufactured reproducibly.

- Specifications

The active substance specification includes tests for description, identity of erlotinib (IR), identity of chloride, assay (HPLC), heavy metals, sulphated ash, residual solvents (GC), related substances (HPLC) and particle size.

The specifications reflect all relevant quality attributes of the active substance. The analytical methods used in the routine controls are suitability described. The validation studies are in accordance with the ICH Guidelines. Impurity limits in the specification are justified by toxicology studies.

Results on the certificates of analysis comply with the specifications, and show good uniformity from batch to batch.

- Stability

The stability results of stress, accelerated and long-term studies according to ICH conditions demonstrate the excellent stability of the drug substance. The drug substance is very stable when exposed to accelerated and higher temperatures, humidity, acids, bases, oxygen and light. The results of the long-term and accelerated studies fulfil the proposed specifications and justify the proposed retest period.

Finished Product

- Pharmaceutical Development

The properties of erlotinib hydrochloride suggested that a tablet manufacturing process based upon dry granulation might be suitable for development of a market formulation.

Consideration was given to this in the selection of excipients, which was based on the evaluation with respect to suitability of manufacturing, and stability of two formulations containing a fixed amount of active substance and varying amount of fillers. Stability studies were also performed with four different formulations containing the active substance in combination with different excipients under accelerated conditions of temperature and humidity.

During the development the influence of the particle size distribution on the processability and the dissolution behaviour of the film coated tablets were investigated.

Based upon the pharmacokinetic and toxicological properties observed in preclinical in vivo studies an immediate release formulation was considered appropriate for clinical development.

The proposed formulations have also been used for the batches used in the clinical and pre-clinical studies. The only differences are the use of printing ink.

The small size of the tablets makes it easy for patients to swallow. The film-coating masks the bitter taste of the active ingredient and minimizes direct contact with the active substance.

All excipients chosen are well-known and comply with the Ph Eur, except from the printing ink. Specifications for the printing ink were provided.

The choice and function of the excipients in the final formulation have been described and justified.

These are: lactose monohydrate, cellulose microcrystalline, sodium starch glycolate Type IA , sodium lauryl sulphate , magnesium stearate , colorants and printing ink.

Regarding the TSE compliance of the excipients, it is confirmed that the lactose used is in accordance with the Public Statement (EMEA/CPMP/571/02).

The description and choice of container closure system is in accordance with the CHMP guideline on *Plastic primary packaging materials.* The experience with the active substance and the data from the stability studies performed with the film coated tablets shows that the chosen PVC blister are adequate to support the stability and use of the medicinal product.

- Manufacture of the Product

The proposed commercial manufacturing process involves standard technology using standard equipment: blending, dry granulation, sieving, tabletting, coating, and imprinting.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process, and is satisfactory. The in process controls are adequate for this pharmaceutical form.

The batch analysis data show that the product can be manufactured reproducibly according to the agreed finished product specification.

- Product Specification

The product specifications include tests by validated methods for description, identity tests of erlotinib (HPLC), content per tablet of erlotinib hydrochloride (HPLC, UV), degradations products (HPLC, UV), dissolution (Ph Eur), uniformity of mass (Ph Eur), microbial purity (Ph Eur), and identity tests for titanium dioxide (colour test).

The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for their intended purpose.

Batch analysis data on three batches for each strength confirm satisfactory uniformity of the product at release.

- Stability of the Product

The stability studies were carried out according to relevant CHMP/ICH stability guidelines. Tablets for each strength have been stored under long term and accelerate ICH conditions as well as for photostability at ICH conditions. Photostability results show that the tablets are not sensitive to light. The analytical methods are identical to those for release.

It is confirmed that the start of shelf-life complies with the CHMP guideline *Start of shelf-life of the finished dosage form.*

Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe

3 Non-clinical aspects

Introduction

All of the definitive toxicology and toxicokinetic studies were conducted in accordance with the GLP procedures. Pilot and exploratory toxicology studies were not conducted under GLP procedures but were generally conducted using appropriate protocols and documentation to assure data integrity.

Pharmacology

Erlotinib was studied in various *in vitro* enzymatic and cell-based assays as well as in human tumour xenograft models in athymic mice. A variety of *in vitro* and *in vivo* general and safety pharmacology studies were performed.

- Primary pharmacodynamics (*in vitro/in vivo*)

The primary pharmacodynamics of erlotinib were studied *in vitro* using human colorectal cancer (DiFi), head and neck cancer (HN5), and breast cancer cell lines. Erlotinib potently inhibited purified, full-length HER1/EGFR tyrosine kinase activity with an IC_{50} of 2 nM. The IC_{50} for the inhibition of cellular EGFR tyrosine kinase activity was 20 nM. More than 1000-fold higher concentrations were required to inhibit other kinases such as *c-src* and *v-abl*. Erlotinib also selectively inhibited the recombinant intracellular kinase domain of EGFR, but not that of insulin-like growth factor 1 receptor (IGF-1R), insulin receptor, platelet-derived growth factor receptor beta (PDGFR-β), Met, and CSF-1R. Complete Inhibition of HN5 cell proliferation in cell culture occurred at 250 nM. Flow cytometric analysis of the cell-cycle distribution indicated that the cells were partially blocked in G1. Inhibition of EGFR by erlotinib induced apoptosis in a significant fraction of DiFi cells [18]. According to the applicant, the primary in vivo metabolites of erlotinib, O-demethylated positional isomers OSI-413 and OSI-420 (also referred to in the development as CP-373,420), also have EGFR tyrosine kinase inhibitory activity and in vivo tumor growth inhibitory activity. Inhibition of EGFR tyrosine kinase activity (IC_{50}) OSI-420, OSI-413, and OSI-943 was 2.5 nM, 1.4 nM, and not determined, respectively. Inhibition of cellular EGFR tyrosine kinase activity (IC_{50}) was 14 nM, 8 nM, and 24 nM, respectively.

The cell-cycle effects of erlotinib hydrochloride were studied in human tumour xenografts in athymic mice where the incorporation of 5-bromodeoxyuridine (BrdU) was monitored by immunohistochemistry of excised tumor samples. Groups consisting of 4 tumor-bearing mice each were administered a single dose of erlotinib in 6% captisol / water, by IP bolus injection or PO. Two hours prior to tumor harvest, 10 mg/kg BrdU was administered IP. Tumors and gut tissue were harvested from 4–96h post erlotinib dose, and relative changes in BrdU incorporation were determined. In the case of duodenum, the labelling index nadir occurred at 8-24 hours for both IP and OS administration, and recovered by 24-48 hours. Each tumor reached the nadir of BrdU incorporation at different times, between 8-72 and 4-48 hours, for IP and PO administration, respectively, and returned to predose levels by 48, and 8-72 hours, respectively. Since the incorporation of BrdU occurs during S phase of the cell cycle, the BrdU incorporation profile reflects the duration of inhibitory effects exerted by erlotinib on DNA replication and cell cycle progression

The dynamics of EGFR-receptor inhibition were evaluated in athymic human tumour xenograft-implanted mice dosed orally with erlotinib. Erlotinib at plasma concentration of 8 μM potently

reduced EGFR associated tyrosine phosphorylation within 1 hour of dosing. The effective dose for 50% inhibition of the target receptor (ED_{50}) was 9.9 mg/kg. On average, a 70% reduction in EGFR-associated phosphotyrosine over a 24-h period was observed after a single 100 mg/kg dose. Substantial growth inhibition of human tumor xenografts was achieved with PO doses of the compound (ED_{50} = 10 mg/kg/day for 20 days). At 92 mg/kg/day HN5 tumour growth was 80% inhibited. Against well-established HN5 tumors (> 1 cm in diameter), treatment with ≥11 mg/kg/day erlotinib either arrested growth or slightly decreased the size of tumors during the dosing period. Treatment with erlotinib produced tumour stasis during and somewhat beyond cessation of dosing. [21].

Xenograft studies on the effect of combining erlotinib with gemcitabine or cisplatin were also submitted, and reports have been published [22]. The studies used the human NSCLC cell line A549 (a slow growing cell line with doubling time of approximately 10 days). The agents were combined at their maximum tolerated doses (MTD, erlotinib at 100 mg/kg daily po, gemcitabine at 120 mg/kg/day every 3 days IP, cisplatin at 6 mg/kg/day every 6 days IP) and at suboptimal doses representing ¼ MTD for both erlotinib and the chemotherapeutic agents. Single agent activity of each agent at its respective MTD was observed. Significant tumor growth inhibition was seen in the gemcitabine/erlotinib and cisplatin/erlotinib combinations (>100% and 90%, respectively), with partial regressions. The enhanced tumor growth inhibition obtained when erlotinib was combined with either gemcitabine or cisplatin was significant compared to that obtained with monotherapy ($p<0.05$). However, treatment of human xenograft tumor bearing nude mice with erlotinib in combination with either gemcitabine or cisplatin resulted in lethal toxicities when each of the drugs was dosed at the respective MTD. When ¼ MTD of erlotinib were administered in combination with sub-optimal doses ¼ MTD of either of the conventional chemotherapeutic agents, tumor growth inhibition was found to be synergistic and treatment was well tolerated. However, the combination therapy regimens were not significantly superior to either of the monotherapy treatments in which each single agent was administered at its respective MTD.

Solid tumor xenograft studies were performed with combination therapies, which consisted of erlotinib plus cisplatin, gemcitabine, or paclitaxel. The major aim of these studies was to examine the effects of sequencing the treatment regimes of chemotherapeutics and erlotinib in various combinations and explore potential differences in efficacy. There appeared to be no clear difference in efficacy in any of the dose-sequence studies. The dosing of erlotinib before the administration of the cytotoxic drug did not have any antagonistic effects. However, there appeared to be greater toxicity when both agents were dosed on the same day, irrespective if one was dosed prior to the other.

- Secondary pharmacodynamics

In vitro tissue bath studies, a ligand binding profile, and *in* vivo mouse CNS activity studies were performed as part of the initial general pharmacology evaluation of erlotinib. The affinities of erlotinib for 67 receptors and other binding sites were determined with radiolabeled ligand. Erlotinib interacted with low affinity on peripheral benzodiazepine (IC_{50}= 2.5 μM), adenosine-1 (IC_{50} = 6.8 μM), and μ-opiate (IC_{50} = 7.0 μM) receptors. Binding occurred at concentrations 125-fold higher than the IC_{50} concentration required to inhibit EGFR tyrosine kinase in intact cells (20 nM) and at concentrations at least 1250 x higher than the IC_{50} for inhibition of purified EGFR tyrosine kinase (2 nM). At concentrations up to 1 μM, erlotinib did not significantly inhibit the binding of ligands to any of the other 64 neurotransmitter receptors, regulatory binding sites, calcium channels, opioid receptors, or neurotransmitter uptake sites tested. In isolated tissue bath studies, erlotinib had no effect on norepinephrine-stimulated contraction of isolated guinea pig aorta or on oxytocin-stimulated contraction of isolated rat uterus. Erlotinib at 10 μM reduced the basal beating rate of isolated guinea pig right atria by 10% compared with vehicle-treated control atria, but had no effect on histamine-induced increase in beating rate. The force of histamine-induced contraction of isolated guinea pig ileum was reduced 42% by 10 μM of erlotinib. The force of Ca^{++}-mediated contraction of K^{+}-depolarised guinea pig ileal longitudinal muscle was reduced 34% by 100 μM of erlotinib. Therefore, the applicant concluded that the inhibitory effect of erlotinib on histamine-induced contraction of isolated ileum was probably not due to calcium channel antagonism. Erlotinib blocked potassium current through recombinant hERG channels with an IC_{20} of 3 μM, or approximately 1170 ng/ml. Erlotinib at 3 μM had no effect on the action potential duration, amplitude, maximum upstroke velocity, or resting membrane potential in rabbit Purkinje fibres.

In studies on pentylenetetrazole-induced convulsions in mice, erlotinib (up to 100 mg/kg) was neither proconvulsant or anticonvulsant.

- Safety pharmacology

Erlotinib dose-dependently inhibited gastric emptying in rats after either oral (5, 10, and 50 mg/kg) or intravenous (I.V.) dosing (2.5, 5 and 10 mg/kg). In rats, erlotinib up to 50 mg/kg orally had no biologically significant effect on renal function, blood gases, blood pH, mean arterial pressure, or heart rate.

Oral administration of 1 to 320 mg/kg of erlotinib to mice did not induce behavioural changes. Mice given a 1000 mg/kg dose had reduced spontaneous locomotor activity in their individual cubicles at the 30 min timepoint, but had normal activity levels when transferred to the open field. One of 3 mice fell from the inverted screen at 1 and 2 hours after dosing, suggestive of impaired coordination and/or decreased grip strength. There were no deaths in any group. In parallel pharmacokinetic studies, plasma concentrations of erlotinib reached a mean C_{max} of 34000 ng/ml within 30 min after the 320 mg/kg dose. The applicant concluded that the behavioural studies indicated that erlotinib was well tolerated by mice at plasma concentrations at least 11 times greater than the estimated clinically efficacious plasma concentration.

A test for potential acute neurobehavioral toxicity was performed in female rats dosed orally with 50, 225, or 1000 mg/kg erlotinib hydrochloride. The study was terminated after behavioural evaluations 24 hours after dosing. Two of ten rats in the high dose group had treatment-related, red discoloured urine and erlotinib caused a slight dose-dependent decrease in body temperature. No biologically significant neurobehavioral toxic effects were seen at any dose level.

The pharmacological effects of erlotinib on the respiratory system following a single oral gavage dose of 50-1000 mg/kg in the albino rat were evaluated. Ventilatory parameters (tidal volume, respiratory rate, and derived minute volume) were measured for 15 minutes periods predose, and 2, 6 and 24 hours postdose. No deaths, no adverse clinical signs, and no treatment-related effects on any of the respiratory parameters examined were observed.

The cardiovascular effects were studied in mongrel dogs treated orally with erlotinib at 50 or 100 mg/kg. The 50 mg/kg dose was expected to yield plasma concentrations near clinically efficacious plasma levels, but the measured levels were low, prompting evaluation of the 100 mg/kg dose. Neither 50 or 100 mg/kg erlotinib affected cardiovascular function in dogs. The measured maximal plasma levels (C_{max}) ranged from 0.2 to 2.8 fold the C_{max} plasma concentration of approximately 3 µg/ml following a 150 mg dose of erlotinib. A second telemetry study confirmed these findings relative to a lack of an erlotinib effect on cardiovascular function in dogs. The measured individual maximal plasma concentrations in this study in dogs ranged from 0.5 to 9.9 µg//ml.

- Pharmacodynamic drug interactions

No nonclinical drug interaction studies have been conducted.

Pharmacokinetics

Pharmacokinetic studies were conducted by the I.V. and oral route of administration in mice, rats, dogs, and monkeys. For the first studies, HPLC procedures with ultraviolet detection were used, and later HPLC methods coupled with LC-MS/MS detection were developed, which provided higher sensitivity, selectivity, and throughput.

- Absorption- Bioavailability

Similar pharmacokinetic behavior of erlotinib was observed between mice, rats, dogs, and monkeys following oral administration of erlotinib hydrochloride. Maximum plasma concentrations were reached between 0.5 and 4 hours and the drug was eliminated with a terminal half-life of 1.5 to 3 hours. At doses of up to approximately 100 mg/kg, nonlinear kinetics were generally observed with greater than expected increases in AUC suggesting saturation of metabolism. For higher doses, the opposite effect was observed with either linear kinetics or less than expected increases in AUC and Cmax with increasing dose. This effect is consistent with decreased drug absorption at high doses possibly due to solubility-rate-limited kinetics. Substantial variability was observed in pharmacokinetic parameters in all dose groups, studies, and species. Exposure to erlotinib and metabolites was higher in dogs in the fed vs. fasted state. Substantial differences in erlotinib plasma

exposure were observed between male and female rats, apparently due to differences in CYP3A2 expression between genders and the slower metabolism of erlotinib in female rats by this enzyme.

Repeat-dose studies conducted in rats, dogs, and monkeys generally showed no changes in pharmacokinetic behavior of erlotinib over time.

- Distribution

Tissue distribution was evaluated in athymic nude mice and rats using whole body autoradiography with ^{14}C-erlotinib hydrochloride. In mice with and without HN5 tumour xenografts, tissue distribution occurred rapidly with maximum radiolabel concentrations 1 hour after oral administration. Most tissues including tumour contained similar radioactivity concentrations to that in plasma, with the exception of kidney and liver, which were approximately 2- to 3 fold greater. In HN5 tumor-bearing athymic nude mice, erlotinib penetrated uniformly into HN5 tumors, pancreas, and lungs. The tumor-to-plasma concentration ratio in the murine human tumor xenograft model ranged from 0.3 to 1. Radioactivity in the brain was approximately 6-fold less than observed in plasma indicating decreased penetration across the blood-brain barrier (BBB). Elimination half-life in plasma and most tissues was approximately 3 hours with liver displaying a longer half-life of 5-6 hours. In rats, radioactivity was widely distributed into tissues after oral administration, with peak concentrations around 4 hours postdose. Radioactivity was rapidly eliminated by both the renal route and via biliary secretion into the gastrointestinal tract. Only limited BBB transfer occurred. Melanin binding of radioactivity was observed. The decrease in radioactivity in pigment containing tissues in pigmented male rats was slow between 24 and 72 h.

Plasma protein binding of erlotinib was evaluated for mouse, rat, dog and human plasma with values of 95%, 92%, 85%, and 92% respectively. Similar experiments with the active metabolite OSI-420 gave values of 73%, 77.5%, 83.3%, and 90.9%, respectively.

- Metabolism (*in vitro/in vivo*)

In liver microsomes from several species, erlotinib had a faster turnover in human and mouse compared to rat and dog. Five metabolites were identified by LC-MS/MS: OSI-413, OSI-420 (most abundant in mouse), OSI-356 (most abundant in human and rat), OSI-493 and OSI-943. In the standard LC-MS/MS assays, the isomers OSI-420 and OSI-413 were not separated and reported as OSI-420/413. O-demethylation products of OSI-356 and OSI-493 were found with rat liver microsomes after induction by phenobarbital, concomitant with a higher metabolic turnover, which indicated metabolism by CYP3A isoenzymes. Furthermore, metabolic stability of erlotinib in β-naphthaflavone-induced rat liver and lung microsomes correlated with the activity of CYP1A1 as a second, predominantly extrahepatic metabolic pathway. This result was consistent with the potential pulmonary first pass effect in rats, which might indicate a certain role of lung metabolism. Glucuronidation was investigated using liver microsomes from different species. Very low but comparable rates of glucuronidation were obtained only with human and dog liver microsomes.

Following oral administration of ^{14}C-erlotinib to rats, the percentage of total radioactivity in plasma, representing unchanged drug, was 88% in males and 78% in females. AUC values of total radioactivity and unchanged drug were 1.8 and 1.6 fold higher in females than in males. However, C_{max} was higher in males than in females. The gender differences were possibly due to differences in CYP3A2 expression and the involvement of CYP3A isoenzymes in the metabolism of erlotinib. In male and female dogs, unchanged drug amounted to 67% and 74%, respectively, of total radioactivity, indicating larger amounts of circulating metabolites in dogs than in rats. Similar to rats, mean AUC values of total radioactivity and unchanged drug were 2.3 and 2.5 fold higher in females than in males. In samples obtained 1-8 hours after oral administration, the same metabolites in almost same relative amounts were detected in male and female rats. OSI-420 was the main metabolite (14%), followed by OSI-493 and OSI-356. In dog plasma, almost similar percentages of OSI-420/413 (11-12%) and low amounts of OSI-356 were found. In mouse plasma, OSI-420/413 was the most abundant metabolite. In tumour samples from mice treated orally, the product of O-demethylation of OSI-356 was the most prominent metabolite.

In rats, dogs, and also in humans, the absorbed erlotinib was extensively metabolised. The metabolite pattern in human excreta was very similar to rats and dogs. Biliary excretion was predominant, and no gender-related differences were seen. In rats, only 4.5% of the dose was excreted into bile as unchanged drug. In all species, urinary excretion was minor with no preference for a specific

metabolite. The radioactivity recovered in urine and faeces as percent of the dose was 89% in rats and 100% in dogs. The most important excreted metabolites in rats were the phase I products OSI-493>OSI-420>OSI-356, comprising together 63% of the dose. Only low levels of phase II metabolites, 2.2% of sulphate of OSI-356 but almost no glucuronides, were detected in rat faeces. In rat bile, approximately 29% of excreted radioactivity was assigned to glucuronic acid conjugates of OSI-420>erlotinib>OSI-413>OSI-356. Therefore, most conjugates are probably cleaved in the gut the lumen or during sample extraction and may encompass larger portions of excreted metabolites, which may be the case also in other species. In dogs, more than 60% of the oral dose was excreted in faeces as the acids of OSI-420 and OSI-413. Other prominent metabolites were abundant in the order OSI-420>OSI-493>OSI-356.

- Excretion

In rats and dogs, erlotinib and its metabolites were excreted predominantly via the faeces (>90% of the dose) and only a small amount was recovered in urine (2-6%). Only a small amount of the absorbed dose was excreted as unchanged erlotinib. In rats, both by oral and I.V. administration, recovery was complete and amounted to 97% within 4 days post administration. Similarly, in dogs dosed orally, excretion was complete (100%) within 6 days post administration.

- Pharmacokinetic drug interactions

The inhibition potential of erlotinib and of OSI-420 on the main human cytochrome P450 isoenzymes was studied *in vitro*. Erlotinib was a strong, reversible, and competitive inhibitor of the glucuronidation of bilirubin. Inhibition parameters were determined using liver microsomes from rat, cynomolgus monkey and human and were equivalent across species. In spite of the strong inhibition of glucuronidation by erlotinib, the potential risk of drug-drug interactions with other glucuronidated drugs appears to be small because of the high apparent Km (24μM, indicating a low affinity/high capacity reaction).

The induction potential of erlotinib on the main cytochrome P450 isoenzymes was studied directly in human hepatocytes. No evidence was obtained that erlotinib has a potential to produce drug-drug interactions by induction of major cytochrome P450 enzymes or transporter proteins.

No in vitro studies on drug-drug interactions were performed.

- Other pharmacokinetic studies

A higher clearance and smaller AUC observed in rats after I.V. versus intraarterial administration indicating first-pass pulmonary extraction. However, the difference in plasma concentrations was mainly in the very first sampling timepoint (5 min) and the AUC of the primary metabolite OSI-420/413 was similar for both routes.

PK of pregnant female rats on the first day of oral administration were similar to studies in non-pregnant females. Increased erlotinib plasma clearance was observed in nursing rat dams. In rabbit, study, comparison between gestation day 7 and 19 showed increased C_{max} and AUC, with the greatest increases in the highest dose group of 1.7 and 2.7 fold, respectively.

Toxicology

- Single dose toxicity

Single dose GLP toxicity studies were conducted in the mouse, rat and dog.

Following single doses, drug-related mortality was seen in rats at 1000 and 2000 mg/kg orally and at 50 mg/kg intravenously. Mortality was seen in mice at 2000 mg/kg orally and at 75 mg/kg intravenously. Death occurred within one to nine days after oral administration or within seconds after intravenous dosing. Commonly observed clinical signs of toxicity following single-dose intravenous administration included decreased activity, irregular respiration, convulsions, rapid chewing, and salivation. The effects of oral treatment were generally delayed (four to six days postdose), and the animals developed an unkempt, thin, hunched, and pale appearance that was accompanied by a loss of body weight or reduced body weight gain.

Single large oral doses (100 to 200 mg/kg) and single intravenous doses (7 and 15 mg/kg) administered to the dog caused numerous abnormal clinical signs, most notably decreased activity, emesis, ataxia, and pupillary dilation. These effects resolved following both oral and intravenous

administration. In addition, oral doses increased serum bilirubin, red blood cell (RBC) indices, activated partial thromboplastin, urinary bilirubin, urinary protein, and decreased lymphocyte counts. Most of these changes resolved within 14 days. There were no histologic alterations 14 days following administration, indicating that a single relatively high oral dose of erlotinib does not produce long lasting adverse effects in the dog.

- Repeat dose toxicity (with toxicokinetics)

Repeat dose GLP and non-GLP oral and I.V. studies were conducted in the mouse, rat, dog and monkey. Rat oral and I.V. studies ranged from 2 weeks to 6 months in duration. Plasma exposures to erlotinib in pre-clinical and clinical studies are summarised in table 1.

In repeat-dose studies, erlotinib was not tolerated at doses of 15 mg/kg/day in female rats or at doses of 50 mg/kg/day in dogs. The primary dose-limiting effects in both species were inappetence with significant weight loss, generalized gastrointestinal toxicity and, in the dog, corneal atrophy and ulceration. All of these effects were reversible upon cessation of treatment. Additional epithelial, toxicity observed in at least one species included effects in skin (follicular degeneration and inflammation, redness, and alopecia), ovary (atrophy), liver (necrosis), kidney (papillary necrosis and tubular dilatation), and gastrointestinal tract (delayed gastric emptying and diarrhea.). Treatment–related increases in ALT, AST, and bilirubin were observed in the 6-month rat and 12-month dog studies.

In addition, erlotinib caused a reduction in red blood cell parameters with a compensatory increase in reticulocytes and an increase in white blood cells, primarily neutrophils. The no-adverse-effect-level (NOAEL) was 1 mg/kg/day in the 6-month rat study and 7.5 mg/kg/day in the 12-month dog study.

In the 6 month study in rat, at 5 and 10 mg/kg/day, the following was seen: females had an increased incidence of ovarian atrophy and minimal to mild papillary necrosis with tubular dilatation of distal convoluted tubules and collecting ducts. Both sexes had dose-related changes in skin and fur, correlating histologically with hair follicular degeneration/inflammation, and dose-related increase in plasma bilirubin and in positive response for haemoglobin in urine. Other findings at 5 and 10 mg/kg/day were dose-dependent ALT increases (indicative of slight liver toxicity), and increased WBC, particularly monocytes and neutrophils (indicative of an inflammatory response). At 10 mg/kg/day, body weight of males was decreased, and in females, there was increased incidence and severity of focal to multifocal liver necrosis, pituitary enlargement, and angiectasis and slight increase in adrenal gland weight. NOAEL was set at 1 mg/kg/day. Plasma concentrations increased with dose though not linearly. Females had higher systemic drug exposure at all doses than males. In conclusion, 5 and 10 mg/kg/day produced follicular degeneration, inflammation in the skin, slight liver toxicity, ovarian atrophy, and renal papillary necrosis. At 10 mg/kg/day, there was decreased mean body weight, (males), increased occurrence of liver necrosis and a marked increase in plasma bilirubin (females). Ovarian atrophy with thickened vaginal and endometrial epithelium is suggestive of a disruption in hormonal control of oestrous cycling. Pituitary enlargement in high dose females is also suggestive of a central drug effect on oestrus cycling. Angiectasis in the female adrenal glands may also be a consequence of the hormonal imbalance associated with ovarian atrophy. Similar toxic effects were observed in I.V. studies in the rat. Reversibility has not been investigated.

Repeat dose oral studies in dogs ranged from several days up to 12 months. Primarily because of emesis observed in the exploratory studies at daily doses of 100 mg/kg/day, doses in the definitive 1- and 12 month studies were determined to be 5, 15 and 50 mg/kg/day.

In the 28-day oral gavage study at 5, 15 and 50 mg/kg/day, emesis, loose stool, and pre-dose skin reddening were occasionally observed in all groups. Salivation was noted at all dose levels. RBC, haemoglobin, and haematocrit values were significantly decreased in the 50 mg/kg/day females. Microscopic evidence of increased numbers of regenerating proximal tubules in the kidney was noted at 50 mg/kg/day. There was no apparent gender difference in plasma concentrations of erlotinib and OSI-420. The NOAEL was set at 15 mg/kg/day.

In the 12-month oral study, doses of 5, 15 or 50 mg/kg/day were given by gastric intubation. Because of unexpected adverse effects, treatment of the high-dose group was modified on day 12 (30 mg/kg/day) and discontinued on day 13. Half of these dogs were euthanised on the following day. The remaining animals underwent a recovery period and were euthanised on day 96. From day 50 onwards, the dose of 5 mg/kg was increased to 7.5 mg/kg and a new group was initiated at 2.5 mg/kg.

This additional group received the compound for 12 months and was euthanised approximately 7 months later than the initial groups. 50 mg/kg induced severe clinical signs and body weight loss, associated with marked histopathological changes to the eyes (corneal atrophy and ulcers), kidneys (papillary necrosis), and digestive tract (inflammation in oesophagus, glandular dilation in duodenum, jejunum, ileum, cecum, and rectum). There were clinical pathology changes related to inflammation (increase in fibrinogen and neutrophils, decrease in albumin). Increased alkaline phosphatase and bilirubin was also seen at this dose but without any associated histopathological findings. There were moderate to marked changes in RBC parameters, decreases in electrolytes and increases in lipids and urea as well as a minimal degeneration of skeletal muscles, attributed to the poor health status of the animals. The ocular changes, body weight losses, haematology, and plasma chemistry changes appeared to be reversible in animals that went through the recovery period. At 15 mg/kg/day and to a lesser extent, at 2.5 and 7.5 mg/kg/day treatment produced reddening of the skin and buccal mucous membrane as well as hair loss. At 15 mg/kg, there was also a reduced mean body weight gain in males.

A non-GLP oral gavage study for up to 14 days in cynomolgus monkeys at 25, 100, 200, and 400 mg/kg/day was performed. In the 200 mg/kg/day group, dosing was discontinued for one animal following nine doses, due to adverse clinical signs of decreased activity, lethargy, sternal/lateral recumbency, dehydration, and reduced food intake. At 200 mg/kg/day for one week, face and/or neck skin or mucosal lesions were observed. At 400 mg/kg/day, a tendency toward decreased food consumption, decreased activity, dehydration, hunched posture, pale skin and lateral recumbency was seen. Slightly decreased RBC parameters and increased reticulocyte counts were observed at 25 mg/kg/day. Increased total bilirubin was noted at 200 and 400 mg/kg/day. At 400 mg/kg/day, slight decreases in lymphocyte counts were noted. Although cutaneous and mucosal changes were observed in the monkeys, histological findings were consistent with minor local trauma and inflammation and were not suggestive of a mechanism-related toxicity or idiosyncratic or allergic reactions. The findings apparently do not correspond to and model skin changes noted in clinical trials with erlotinib.

- Genotoxicity *in vitro* and *in vivo* (with toxicokinetics)

In *in vitro* tests, with and without metabolic activation, erlotinib, the impurity RO0729853-001, or any of the metabolites, were not mutagenic in the microbial reversion assay, did not produce chromosomal damage in human lymphocytes, and did not produce a biologically significant dose-dependent mutagenic response in the CHO/HGPRT assay. *In vivo*, erlotinib did not induce chromosomal damage as evidenced by micronucleus formation in the bone marrow cells of male or female CD-1 mice following three daily oral doses of up to 1000 mg/kg/day.

- Carcinogenicity (with toxicokinetics)

Carcinogenicity studies were not performed.

- Reproductive and developmental studies

A series of tests was conducted to evaluate the effects of erlotinib on male and female fertility in the rat, embryotoxicity and teratogenicity in the rat and rabbit, and pre- and postnatal development of the rat (data not shown). Erlotinib at doses that produced maternal toxicity and decreased pup survival in the rat was not teratogenic, and did not affect the development of F1 or F2 generations. Erlotinib at doses that produced maternal toxicity and embryotoxicity in the rabbit was not identified as a selective developmental toxicant. In rats, maternal toxicity was seen at doses of ≥5 mg/kg/day and foetal toxicity was seen at doses of ≥10 mg/kg/day. In rabbits, maternal and foetal toxicity was both observed at ≥25 mg/kg/day.

- Local tolerance

Following dermal exposure for 24 hours, very slight erythema was produced in one of six rabbits at 2000 mg/kg. Testing of 54.3 mg erlotinib in a volume of 0.1 ml introduced into the rabbit eye indicated that erlotinib is not an ocular irritant in rabbits. Based on a guinea pig skin sensitisation test, the sensitisation potential of erlotinib was categorised as mild according to the Kligman/Magnusson classification scheme.

- Other toxicity studies

Phototoxicity studies

Erlotinib is an UV-absorbing compound that is present in eye and skin following systemic exposure. Erlotinib was given to hairless rats P.O. for 7 days at 5 mg/kg/day, and produced a weak although discernible phototoxic skin reaction *in vivo* in the hairless rat. Erlotinib was not phototoxic *in vitro* in 3T3 fibroblasts at concentrations that were limited by solubility.

Effects on bilirubin excretion

In anaesthetised male rats, erlotinib was administered via a jugular catheter as a slow bolus of 1, 5 or 15 mg/kg. Erlotinib at 5 and 15 mg/kg consistently reduced both total and direct bile bilirubin at all measured timepoints with no change in bile flow rate. At 1 mg/kg there was only a transient decrease at 30 minutes post-dose. Serum bilirubin was increased at 5 mg/kg (approximately 3-fold) and at 15 mg/kg (approximately 5-fold). Plasma concentration of parent compound and of the primary metabolite reached a maximum 30 minutes post-dose, declining steadily from this point. No effect on liver weight was observed. A NOEL was not established. In *in vitro* studies, erlotinib inhibited microsomal glucuronidation of bilirubin and suggested that this inhibition was similar across species (see page 15, Pharmacokinetic drug interactions).

Immunotoxicity

Special immunotoxicity and antigenicity studies have not been conducted on erlotinib.

Studies on impurities

To ensure qualification of the specified impurity CP-471-125, bacterial reverse mutation and chromosomal aberration tests with human peripheral blood lymphocytes were conducted. Both tests were negative under GLP test conditions.

Ecotoxicity/environmental risk assessment

Considering ecotoxicological and environmental fate properties as well as use pattern, dosage and maximal estimated amounts of erlotinib to be placed on the market, no exposure levels of concern to the environment are to be expected.

Discussion on the non-clinical aspects

Pharmacology

The primary *in vitro* pharmacodynamics studies showed that erlotinib is a potent, selective, direct-acting inhibitor of the EGFR tyrosine kinase catalytic domain. The primary *in vivo* metabolites of erlotinib also have EGFR tyrosine kinase inhibitory activity. The antitumor effects of erlotinib in several xenograft models correlated well with inhibition of tumor-associated EGFR phosphotyrosine.

According to the applicant the data on drug exposure and antitumor response in human tumor xenograft models suggested evaluation of clinical dosing schedules designed to produce total plasma erlotinib concentrations of $\geq$ 420 ng/ml. An erlotinib value of 11000 ng/ml would correspond to plasma concentrations producing 80% inhibition of tumour growth in the xenograft models.

Most *in vitro* and *in vivo* general and safety pharmacology studies did not indicate that erlotinib produced non-target pharmacological effects that would cause specific safety concerns for clinical use. Binding of a few among a large panel of receptors, only occurred at concentrations at least 125-fold higher than the IC_{50} concentration required to inhibit EGFR tyrosine kinase in intact cells. Erlotinib dose-dependently inhibited gastric emptying in rats, which can be seen as a class effect.

A number of mutations have been identified in the EGFR gene. Tumour response and acquired drug resistance towards EGFR TK inhibiting agents has been associated with specific mutations within the EGFR gene [18, 23-31]. The functional consequences of these mutations on receptor function and their importance for tumour growth are not yet understood in detail. The applicant is planning to address the issue from a clinical perspective and no further mechanistic *in vitro* and *in vivo* studies are planned.

Pharmacokinetics

The pharmacokinetic behaviour of erlotinib has been adequately investigated. In summary, erlotinib was widely distributed into tissues including tumour tissue. Concentrations were smaller in the brain than in plasma. Erlotinib was extensively metabolised and rapidly eliminated mainly via biliary

secretion into the gastrointestinal tract, and excreted predominantly via the faeces together with its metabolites. The contribution of lung to the overall metabolism of erlotinib appears to be low.

CYP1A1, CYP1A2 and CYP1B1 might contribute to erlotinib clearance especially after induction by smoking [32] (see also Clinical Pharmacokinetics, and Discussion on Clinical Pharmacokinetics).

Toxicology

Erlotinib toxicity predominantly in epidermal tissues. The major target organs were kidney, liver, skin, GI tract, ovaries and cornea. Treatment–related increases in ALT, AST, and bilirubin were observed in the repeat-dose studies studies at exposure levels well below exposure levels in man. The increase in bilirubin apparently was caused by erlotinib impairment of bilirubin conjugation and excretion associated with specific inhibition of UDPglucuronosyltranferase.

When applying higher dose levels (50 mg/kg/day) in the dog repeat dose study, unacceptable toxicity was noted. Exposures obtained in repeat dose toxicity studies compared to the human exposures were not sufficiently high to calculate exposure multiples, and thus, safety margins are non-existent.

Erlotinib was not genotoxic. The lack of carcinogenicity studies has been adequately justified with reference to relevant guidance [33, 34].

Reproductive toxicity has been observed with erlotinib, and this is adequately reflected in the SPC (see section 5.3). The EGF receptor plays an important role in embryonic development. Blockade of this receptor is a potential risk on abnormal embryonal and foetal development. As such, erlonitib, has the potential to be a teratogen. Embryonal and foetal toxicity were observed in rats and rabbits. Embryonal and foetal toxicity is expected in humans at therapeutic exposure. Erlonitib should therefore not be used during pregnancy unless clearly necessary. It is not known whether erlotinib is excreted in human milk. Because of the potential harm to the infant, mothers should be advised against breastfeeding while receiving Tarceva. Adequate information has been included in the SPC (see section 4.6), and package leaflet.

A mild phototoxic reaction has been observed in rats. Severe phototoxicity in humans is unlikely. Adequate information has been included in the SPC (see section 5.3). Photogenotoxicity and photoallergy studies are not required, since erlonitib hydrochloride shows photostability (see Quality Aspects).

Inhibition of EGFR signalling augments the inflammatory response by increased chemokine expression and heavier inflammatory cell infiltrate involving T lymphocytes (Mascia et al., 2003). No effect on lymphoid or myeloid organs was seen in toxicity studies after up to 12 months of erlotinib exposure. Based on the results of the standard toxicity studies, additional immunotoxicity and antigenicity studies are not required [35].

4 Clinical aspects

The clinical documentation for the submission comprised 17 phase I trials (PK, metabolism and interactions), of which 9 were performed in healthy volunteers and 8 in patients with solid tumours. Thirteen phase I-IIa studies were performed in patients with solid tumours (dose-ranging, safety and PK). The marketing authorisation application was based on one randomized placebo-controlled phase III study (BR.21, N=731) conducted in patients with Stage IIIB/IV NSCLC after failure of at least 1 standard chemotherapy regimen. Reference was also made to two randomised studies evaluated erlotinib used in combination with standard chemotherapy in first-line therapy for NSCLC. All studies in the erlotinib clinical development program were performed in concordance with ICH GCP.

The recommended daily dose of Tarceva is 150 mg taken at least one hour before or two hours after the ingestion of food (see SPC section 4.2). When dose adjustment is necessary, reduction should occur in 50 mg steps (see SPC section 4.2 and 4.4). Tarceva is available in strengths of 25 mg, 100 mg and 150 mg. In summary, concomitant use of CYP3A4 substrates and modulators may require dose adjustment (see discussion on clinical pharmacokinetics, and SPC section 4.2 and 4.5). Tarceva is contraindicated in case of severe hypersensitivity to erlotinib or to any of the excipients.

Clinical Pharmacology

- **Pharmacokinetics**

The pharmacokinetics of erlotinib has been studied in healthy subjects and in cancer patients. Analyses of erlotinib and the metabolite OSI-420 were carried out primarily by LC-MS/MS methods. Single dose and multiple dose plasma PK parameters in healthy volunteers are summarised in tables 2 and 3.

The studies in healthy subjects were performed in males and females, but females formed a minority. The mean ages in the healthy-volunteer studies were generally between 26 and 38 years. The majority of the recruited subjects were Caucasians. Black, Hispanic and Asian individuals however were also studied. Several pharmacokinetic studies were performed in patients with various solid tumours, mostly NSCLC. The mean age in the patient studies was higher than in the populations of healthy volunteers and roughly varied between 55 and 65 years. The patients studied included women as well as men. One specific study was performed in Japanese patients (Study JO16564).

Table 2. Erlotinib Single Dose Plasma PK Parameters in Healthy Volunteers, Median (min-max)

Study	Dose mg (Fed/fasted)	Formulation No. of Subjects	C_{max} (µg/mL)	T_{max} (h)	$AUC_{0\rightarrow\infty}$ (µg*h/mL)	$t_{½\lambda z}$ (h)
248-001	3 (fasted)	Solution 4	0.0149 (0.0100-0.0243)	0.8 (0.5-1.0)	NC	NC
	10 (fasted)	Solution 4	0.0885 (0.0658-0935)	1.0 (0.5-2.0)	0.496 (0.365-0.586)	3.43 (1.87-4.59)
	30 (fasted)	Solution 4	0.460 (0.251-0.507)	0.5 (0.5-1.0)	2.22 (1.73-2.83)	5.83 (3.39-8.76)
	100 (fasted)	Suspension 4	0.971 (0.857-0.990)	1.5 (0.5-3.0)	10.0 (9.00-12.8)	6.21 (5.84-7.44)
	300 (fasted)	Suspension 4	2.40 (1.83-2.89)	2.5 (2.0-3.0)	37.6 (32.5-42.9)	9.04 (7.78-10.9)
	1000 (fasted)	Suspension 4	5.93 (3.68-6.90)	4.0 (1.0-18.0)	126 (90.4-176)	7.70 (6.82-18.1)
	200 (fasted)	Tablet 3	1.54 (0.792-2.41)	2.0 (1.0-2.0)	22.9 (11.6-30.9)	9.04 (5.31-9.54)
	200 (fed)	Tablet 3	1.58 (1.29-2.00)	2.0 (2.0-4.0)	23.6 (21.0-29.5)	6.32 (6.08-6.73)
248-002	200 (fasted)	Tablet 3	0.963 (0.638-1.70)	2.5 (1.0-4.0)	21.1 (10.2-29.7)	8.8 (7.8-11.1)
NP16584	150 (fed)	Tablet 9 (Period 1 only)	1.34 (0.958-1.71)	3.0 (1.0-6.0)	20.3 (18.6-24.6)	9.0 (6.0-11)
NP16584	150 (fasted)	Tablet 9 (Period 1 only)	0.704 (0.535-1.43)	3.0 (1.5-4.0)	10.3 (4.97-17.7)	7.0 (4.1-11)
NP16638	150 mg (fasted)	Tablet 24 (Group 1 and 2 combined)	1.31 (0.475-2.44)	1.5 (1.0-6.0)	17.6 (6.63-33.2)	8.49 (4.14-17.8)
NP16612	100 mg (fasted)	Tablet 24 (Group 1 and 2)	0.628 (0.199-1.31)	2.0 (1.0-24)	11.1 (3.52-21.2)	8.49 (4.77-15.3)
OSI2716g	150 mg	Capsule 37 (Arm A)	1.39 (0.635 – 3.00)	2.12 (1.00-5.02)	25.87 (9.71-67.42)	14.39 (6.27-48.03)
	150 mg	Capsule 18 (Arm B)	1.335 (0.933-2.520)	2.015 (1.00-4.00)	33.51 (19.29-70.32)	18.96 (7.63-49.09)

NC -= not calculated

Table 3. Erlotinib Multiple Dose Plasma PK Parameters in Healthy Volunteers, Median (min-max)

Study	Tablet Dose mg (Fed/fasted)	No. of Subjects	C_{max} (µg/mL)	T_{max} (h)	Clss/F L/h	AUC $_{0\rightarrow tau}$ (µg*h/mL)	Rac (h)
248-002	200 mg BID	5	NC	NC		NC	5.4 (5.0-12)
NP16787	100 mg QD (fasted)	8 (Day 7)	1.10 (0.575-1.52)	3.5 (1.0-4.0)	7.9 (4.5-14)	12.7 (7.13-22.2)	2.1 (1.5-4.5)
NP16787	100 mg QD (fed)	6 (Day 7)	1.45 (0.892-1.92)	4.0 (3.0-6.0)	6.9 (3.0-8.9)	14.56 (11.3-32.9)	2.0 (1.7-2.2)
NP16793	150 mg (fasted)	6 (Day 7)	1.09 (0.742-1.31)	4.0 (3.0-6.0)	10 (6.8-14)	15.2 (10.4-22.1)	1.5 (1.3-2.6)

NC = Insufficient data for calculation.

Rac = accumulation index.

[a] Trough samples only were collected for the multiple dose portion of the study.

- Absorption

Two bioavailabilty studies were conducted with erlotinib 100 PO QD × 8 and 150 mg PO single dose, respectively, in fed and fasted in healthy subjects (N=21 each). Two bioavailability and bioequivalence studies were conducted to assess absolute BA and establish BE of multiple tablet strengths.

After oral administration, erlotinib peak plasma levels are obtained in approximately 4 hours after oral dosing. In the absolute bioavailability cross-over study of a single 150 mg oral dose compared to an IV 30-minutes infusion of 25 mg, different terminal half-lives of 21 and 13 hours were observed, respectively, in normal healthy volunteers. A mean estimate of oral bioavailability for the 150 mg tablet of 59% (95% CI: 55% – 63%) was obtained using NONMEM, taking into account the faster clearance of erlotinib observed at the lower IV dose.

A high calorie, high fat meal increased the oral bioavailability of erlotinib both after a single dose (study NP16584) and after multiple doses (study NP16787). In study NP16584 subjects received 2 single 150 mg erlotinib doses, one in the fasted state and the other after a high fat, high calorie breakfast in a randomized sequence with a 7-day washout period. Tmax was similar when erlotinib was administered with food. Tlag was increased by approximately 0.5 hour. There was a 109% increase in erlotinib AUC0-∞ and a 64% increase in Cmax in the fed state as compared to fasted conditions. The mean pharmacokinetic parameters for the metabolite OSI-420 in Period 1 indicated a 98% increase in AUÇand a 32% increase in Cmax when study drug was administered in the fed state (compared to fasted conditions). Tmax was increased by approximately 1 hour. Patients had higher Cmax and AUC0-24 than subjects.

At doses ranging from 100 mg to 1000 mg, AUC increases linearly with no observable saturation in its elimination. Linearity may change from very low doses (< 50 mg) to higher dose ranges (100 to 1000 mg), although data at low doses are limited. Mean (± SD) terminal half-life at 25 mg IV and 150 mg oral doses were 13 (± 6) and 21 (± 10) hours, respectively. The exact mechanism or specific pathway that may be saturated at the low dose range is not known.

There was a high inter-subject and inter-study variability in clearance and plasma terminal half-life of erlotinib estimated across several healthy volunteer studies. Median clearance ranged from 5.27 to 15.0 L/h and half-life ranged from 7.0 to 16.3 hours among 6 studies in a total of 110 subjects at doses ranging from 100 to 200 mg. From various healthy volunteer studies, within-subject CV for AUC varied from 16% to 24% while for Cmax, it ranged from 29% to 38%, as estimated in three different studies. The CV for the primary metabolite (OSI-420) was comparable with those of parent erlotinib. In general, cancer patients appeared to have higher AUC and longer plasma terminal half-life than

healthy subjects after a single dose. Exposure also appeared higher in the target population following repeated administration.

- Distribution

Erlotinib was administered to healthy volunteers (4 males, 16 females) as a 25 mg short IV infusion, the steady state volume of distribution (Vss) was estimated to be moderately high (mean ± SD: 83.84 L ± 17.56; n = 18).

In vitro studies showed that erlotinib is highly bound in blood with 96.5% bound to blood components. Binding of erlotinib was divided in 2 components: 34.2% to the blood cells and 62.37% to the plasma proteins when the hematocrit was 0.48. The free fraction (fu) was 3.5%. Erlotinib was bound primarily by albumin and non-esterified fatty acids, which comprise 43.9% of the total blood binding or 70.4% of the plasma protein binding. Erlotinib binding to alpha-1 acid glycoprotein (AAG) was found to increase at higher AAG concentrations with values of 52.3% at 0.38 mg/mL and 96.3% at 5 mg/mL.

Tumour-to-plasma erlotinib ratio was measured in a study of 4 patients (3 with NSCLC, and 1 with laryngeal cancer) receiving 150 mg daily oral doses of Tarceva. Tumour samples from surgical excisions on Day 9 of treatment revealed tumour concentrations of erlotinib that averaged 1,185 ng/g of tissue. This corresponded to an overall average of 63 % (range 5-161 %) of the steady state observed peak plasma concentrations. The primary active metabolites were present in tumour at concentrations averaging 160 ng/g tissue, which corresponded to an overall average of 113 % (range 88-130%) of the observed steady state peak plasma concentrations. The active metabolite OSI-420 was present in the tumour at concentrations similar to the observed steady-state Cmax in plasma (88% to 130%).

- Elimination

Erlotinib is excreted predominantly as metabolites via the faeces (>90%) with renal elimination accounting for only a small amount (approximately 9%) of an oral dose. Following administration of a single dose of [14C]-erlotinib as a 100 mg suspension to 4 healthy male subjects, plasma concentrations of erlotinib, OSI-420, and total radioactivity peaked at 1.4 hours after oral administration. The total radioactivity values were only slightly higher than the parent drug (erlotinib), suggesting that circulating radioactivity was primarily attributable to unchanged drug. In contrast, less than 2% of the administered dose was excreted as unchanged drug in urine and feces.

Based on the structures of the metabolites, 3 primary routes of metabolism were identified: O-demethylation of the side chains followed by oxidation to the carboxylic acid, oxidation of the acetylene moiety followed by hydrolysis to the aryl carboxylic acid, and aromatic hydroxylation of the phenyl-acetylene moiety. Conjugates of OSI-356 with sulfuric or glucuronic acid as well as O-glucuronides of OSI-413/420 and its further de-alkylated products were found in small amounts.

The elimination of erlotinib was primarily metabolic with little or no direct elimination via kidney or biliary excretion.. The identified metabolites accounted for > 80% of the total radioactivity recovered in urine and feces.

Four major metabolites were found in plasma. The bioanalytical LC-MS/MS assay cannot distinguish between the isomers OSI-413 and OSI-420. These two metabolites possess similar EGFR inhibitory pharmacological activity compared to the parent compound. In human plasma, these metabolites accounted for approximately 5% of the amount identified as erlotinib with a variable effective mean ratio of OSI-420: OSI-413 between 2:1 and 4:1. The primary metabolite does not possess potential for P450-based drug-drug interactions as based on in vitro studies.

In vitro studies using human liver microsomes and specific CYP inhibitors, as well as recombinantly expressed human cytochrome P450 enzymes revealed that erlotinib is metabolised in humans in the liver primarily by CYP3A4 and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung, and CYP1B1 in tumour tissue also potentially contribute to the metabolic clearance of erlotinib. Potential interactions with implications on erlotinib exposure may occur with drugs which are metabolised by, or are inhibitors or inducers of, these enzymes. CYPs 1A1, 3A4, and 3A5 catalyzed the formation of OSI-413, OSI-420, OSI-356, and OSI-493, with OSI-356 being the most prominent form produced by CYP3A4 and CYP1A1, but a more pronounced formation of OSI-420 by CYP3A5 and of de-methylated OSI-356 by CYP1A2. Inhibition of

microsomal metabolism by 10 μM ketoconazole revealed 80% to 95% inhibition of the formation of the different metabolites.

- Special populations

Population PK analyses were performed first using data from 2 Phase III trials of erlotinib in combination with platinum doublet (Studies BO16411 and OSI2298g) and later using data from single Phase III trial with erlotinib given as monotherapy (Study BR.21) in NSCLC patients. Data from several Phase II trials were also combined in both analyses.

For the combination data set, A 1-compartment model with first-order absorption and elimination well described the concentration-time data of the parent drug. The ratio of the AUCs of metabolite/parent calculated from the model was 12.1%. A total of 18 covariates were evaluated for erlotinib CL and V_c. Total bilirubin (TBIL) and AAG were the covariates most critical to explaining inter-individual variability for CL. Compared with the population median, patients with TBIL levels in the 95th percentile (1.1 mg/mL) had a change in CL of -27.7% (CV% of approximately 50%). Compared with the population median, patients with AAG levels in the 95th percentile (2.3 g/L) had a change in CL of -15.9%. Other covariates such as gender, alkaline phosphatase, creatinine clearance, and chemotherapy status had minimal effects on CL. Using erlotinib monotherapy as a reference, CL was 10.5% and 18.1% faster in patients treated with erlotinib in combination with carboplatin/paclitaxel and cisplatin/gemcitabine, respectively. The estimated CVs were large (> 44%). Inter-individual variability for CL and V_c in the final model was 40.5% and 64.3%, respectively, compared with 50.9% and 80.6% in the base model. The covariate effects in the final model explained about 37% of the inter-individual variance for CL and 36% of the inter-individual variance for V_c.

The single-agent dataset for the analysis included 2576 concentration measurements from 591 patients, of which 252 patients were from 4 Phase II single-agent trials (Studies A248-101, A248-1003, A248-1007, and OSI2288g) and 339 patients were from the single-agent Phase III trial (Study BR.21). The structural model and the final model previously developed were applied to the single-agent dataset. In addition, the effect of enzyme inducers/inhibitors and the effect of smoking, which were not included in the previous model, were also assessed.

Current smokers had faster clearance than patients who had never smoked or former smokers; therefore, the smoking effect was included in the final model for the single-agent data. In contrast, co-administration of enzyme inducers, which was found to be significantly associated with clearance (CL/F), was not incorporated in the single-agent final model because < 1.5% (n = 9) of the cases were well documented. In addition, alkaline phosphatase, which had a small effect in the previous model, was not tested with the single-agent data because alkaline phosphatase measurements were missing for 305 of 339 patients.

Overall, in the single-agent final model, the effects of covariates such as gender, albumin, and creatinine clearance were similar to those estimated in the first population PK analysis; all had a small effect on CL. Total bilirubin and AAG remained to be the most significant covariates. The effect of AAG was slightly greater than that previously reported, with an increase in AAG associated with a decrease in erlotinib clearance.

According to the single-agent final model, the PK parameters for the typical patient were 3.95 L/hr for CL/F, 233 L for volume of distribution of the central compartment (V_c/F), and 40.9 hours for terminal half-life ($t_{1/2}$). The coefficient of variation (%CV) for inter-individual variance for CL/F and V_c/F was 39.4% and 71.7%, respectively. The individual PK parameters for all patients were estimated from the single-agent final model using a Bayesian approach. No marked differences in the PK parameters were found across the different studies. Values for CL/F and V_c/F for Study BR.21 patients were within the ranges for the other studies. Mean values indicated a slightly lower CL in patients in the BR.21 study compared with patients from other studies, whereas V_c/F was similar. Based on the individual PK parameters from 591 patients, the predicted mean for steady-state area under the concentration–time curve (AUC_{SS}), maximum concentration ($C_{max,SS}$), and minimum concentration ($C_{min,SS}$) were 41.3 ± 22.0 μg • hr/mL, 1995 ± 906 ng/mL, and 1238 ± 826 ng/mL, respectively. Median $t_{1/2}$ for single-agent patients was 36.2 hours, which is consistent with the population estimate of 40.9 hours from this analysis.The pharmacokinetics of erlotinib has not been studied in patients with impaired renal or hepatic function.

Concerning gender, only one study allowed for a meaningful comparison of pharmacokinetics between male and female subjects. A statistically significant difference was observed for AUC and elimination half-life. From the population model, the difference between male and female clearance is 4.70 L/h versus 4.29 L/h. Females consistently achieved a higher exposure but the estimated differences were small (3.7% increase of AUCss and a 5% increase of C24ss).

The single dose pharmacokinetics for erlotinib were compared using data from 2 comparable Phase I trials; one in Japanese NSCLC patients and the other in western cancer patients, in which 50/56 patients were Caucasian, 3 were Hispanic, 1 was Black, and 1 was Asian There was no apparent difference in PK characteristics of erlotinib between Japanese and western patients.

The effect of age on erlotinib pharmacokinetics was evaluated in the pivotal phase III Study BR.21, comparing subgroups aged < 65 years with those ≥ 65 years. The median plasma concentration of the principal erlotinib metabolite, OSI-420, was increased by 58.6% and the sum of erlotinib plus OSI-420 was increased by 17% in the patients who were ≥ 65 years old, compared to younger patients.

The pharmacokinetics of erlotinib has not been studied in children.

- Pharmacokinetic interaction studies

A moderate inhibition of CYP3A4 (~ Ki 8 μM) and CYP2C8 (~ Ki 15 μM) by erlotinib, and a weak inhibition of CYP1A2 (~ Ki 20 μM) and CYP3A4 (~ Ki 24 μM) by OSI-420 were observed. There was no significant inhibition of the activities catalyzed by CYP2C9, CYP2C19 and CYP2D6 or by CYP1B1, suggesting that no drug-drug interactions with xenobiotics metabolized primarily by these CYP450 enzymes is expected. Hence, no clear evidence was obtained to suggest that erlotinib has the potential to produce drug-drug interactions by induction of major cytochrome P450 enzymes or transporter proteins. An interaction study between erlotinib and midazolam in order to differentiate between effects on intestinal and hepatic CYP3A4 is in progress. In *in vitro* studies with human liver microsomes erlotinib was found to be a strong and, reversible inhibitor of the glucuronidation of bilirubin with an app. K_i 1.3 μM. Inhibition was similarly apparent with human recombinant expressed UDP-glucuronosyltransferase UGT1A1 (app. K_i 0.7 μM, substrate bilirubin) but not with other transferases.

Interaction studies in healthy volunteers were performed with a potent CYP3A4 inhibitor, ketoconazole, and a potent CYP3A4 inductor, rifampicin. Rifampicin pretreatment caused a mean decrease in erlotinib Cmax by 29 % and of AUC by about 69% compared with erlotinib alone. Mean oral clearance (Cl/F) of erlotinib was approximately 3-fold higher following rifampicin administration. The corresponding mean terminal half-life was reduced to a small extent (29%) from 8.6 hours (erlotinib alone) to 6.1 hours (rifampicin pretreatment). Ketoconazole had a clear effect on the AUC and Cmax of erlotinib. Exposure to erlotinib in terms of AUC in the presence of ketoconazole was estimated to be increased by 64 % compared with that following administration of 100 mg erlotinib alone. With regard to the Cmax of erlotinib administered concomi-tantly with ketoconazole, exposure was estimated to be increased by 67 % compared with Cmax of erlotinib administered alone. In contrast, there was little change in erlotinib pharmacokinetics on repeat treatment in the control group that did not receive ketoconazole.

No evidence for PK interactions between erlotinib and the different chemotherapies studied: cisplatin, carboplatin, gemcitabine, paclitaxel, docetaxel, or capecitabine were found (data not shown).

Pharmacodynamics

No clinical studies investigating the mechanism of action have been conducted. No clinical primary pharmacology of erlotinib studies have been conducted.

Dose selection

The available preclinical data at the time of dose selection had consistently suggested a dose/response relationship regarding the inhibition of the target according to some published series [18, 36] and data presented by the applicant. Doses below MTD (50 mg/kg/p.o. in Captisol, Balb/c nude mice) were less active than the actual MTD. The recommended dose of erlotinib in phase III trials was, therefore, selected on the basis of the MTD, as determined in the Phase I study, A248-004. After daily dosing, the MTD was observed at the 150 mg dose level. The average trough (C_{min}) concentration at this MTD dose of 150 mg on Days 24 to 29 in this study was 918 ng/mL (median: 746 ng/mL; n=19). This concentration was higher than that (680 ng/mL) observed in HN5 murine model at the dose of 50%

inhibition of tumor growth and was considered adequate to enter into Phase III trials. Assuming a protein binding of 95%, the corresponding unbound concentration (Cf) of drug is estimated to be 34 ng/mL (86 nM). This concentration is 4 times higher than IC50 for cellular phosphotyrosine reduction assays (7.9 ng/mL) and 43 times higher than the IC50 for the kinase assay (0.79 ng/mL). The average steady state trough (Cmin) concentration observed at 150 mg in study A248-004 was 918 ng/mL based on total plasma concentrations and 46 ng/mL based on free plasma concentrations, assuming 95% protein binding.

Secondary pharmacology

Based on the positive hERG results (IC20: 3μM) and current regulatory guidelines, a further investigation of the potential effect of erlotinib on ECG (in particular, QTc) in humans was planned. This study in healthy volunteers was terminated prematurely due to tolerability issues. No effect on the QT-interval could be demonstrated. Subsequently, ECG data collected from 7 healthy volunteer studies with a total of 152 subjects was subject to detailed analysis. All ECG data were reanalysed centrally at an outside laboratory specialising in the high-resolution manual analysis of ECG data and morphological interpretation. Although several of these studies did not have a placebo arm, QTc-interval changes from baseline and maximum QTc-interval changes were evaluated with respect to time after dose, peak plasma drug (and active metabolite, OSI-420) concentrations and AUC to determine the potential relationship of any changes in QTc-intervals with systemic drug exposure.

An integrated meta-analysis was performed of limited data with placebo and the 100 mg, 150 mg, and 200 mg erlotinib doses using Day 1 data from 7 studies. Serial measurements of QTc-intervals over 24 hours after dosing were available in a minimum of 12 subjects at each dose. No effect of erlotinib was seen on mean QTc (F or B)-intervals at any of these doses. An analogous meta-analysis was performed for day 7 multiple dose (steady state) data from 2 studies where subjects received therapeutic doses of 100 or 150 mg erlotinib per day. There was no increase in QTc (F or B)-intervals relative to baseline (pre-treatment on Day 1) despite having 7 consecutive days of dosing.

Discussion on Clinical Pharmacology

Discussion on clinical PK

Food increases the exposure after an oral dose of erlotinib both in terms of AUC and Cmax. The exact mechanism for this effect of food on erlotinib bioavailability is not known. The effect may be of clinical importance, and an appropriate warning has been included in the SPC (see SPC section 5.2)

Having a pKa of 5.4, erlotinib has a greater solubility in acidic media when the pH is less than 5 due to protonation of the secondary amine. The effect of antacids, proton pump inhibitors and H2 antagonists on the absorption of erlotinib have not been investigated. The applicant committed to confirm these results through an in-vivo study to evaluate the effects of antacids, H2 antagonists and proton pump inhibitors. Caution should be exercised when these drugs are combined with erlotinib (see SPC section 4.4).

Erlotinib has a mean apparent volume of distribution of 232 L and distributes into tumour tissue of humans. Erlotinib and its primary metabolite have been located in solid tumours in concentrations approximating that of plasma, though with a large variability. Plasma protein binding is approximately 95 %. Erlotinib binds to serum albumin and alpha-1 acid glycoprotein (AAG).

Erlotinib is metabolised in the liver by the hepatic cytochromes in humans, primarily CYP3A4 and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung, and 1B1 in tumour tissue potentially contribute to the metabolic clearance of erlotinib. Less than 2 % is excreted unchanged in the urine. Minor contributions from CYP3A5 are also possible.

Results of an in vitro study using L-MDR1 (human) and L-mdr1a (mouse) cells show that erlotinib is a substrate for the P-glycoprotein drug transporter (data not shown). Theoretically, rug penetration in the brain may be increased when combined with inhibitors of P-glycoprotein, e.g. cyclosporine, verapamil. However, no major CNS toxicity of erlotinib was observed in large patient trials conducted in NSCLC patients in the presence of various co-medications. Similarly, good tolerability has been reported in various communications on glioblastoma patients with response to erlotinib [37, 38].

A population pharmacokinetic analysis in 591 patients receiving single agent Tarceva show a mean apparent clearance of 4.47 L/hour with a median half-life of 36.2 hours. Therefore, the time to reach steady state plasma concentration would be expected to occur in approximately 7-8 days. No clinically

significant relationship between predicted apparent clearance and patient age, bodyweight, gender and ethnicity were observed. Patient factors, which correlated with erlotinib pharmacokinetics, were serum total bilirubin, AAG and current smoking. Increased serum concentrations of total bilirubin and AAG concentrations were associated with a slower rate of erlotinib clearance; however, smokers had a higher rate of erlotinib clearance. The clinical relevance of these differences is unclear. However, smokers had a higher rate of erlotinib clearance. Based on the results of the population pharmacokinetic study, current smokers should be advised to stop smoking while taking Tarceva, as plasma concentrations could be reduced otherwise. The observed variability of erlotinib exposure and the trend of greater AUC values in female subjects might be due to gender differences in the percentage of non-smoking individuals with apparent intermediate to high CYP1A2 metabolic activity [39].

The safety and efficacy of erlotinib has not been studied in patients with hepatic impairment. Erlotinib is eliminated by hepatic metabolism and biliary excretion. No data are available in patients with hepatic impairment. Therefore caution should be exercised when administering Tarceva to patients with hepatic impairment. Use of Tarceva in patients with severe hepatic impairment is not recommended (see SPC section 5.2). The applicant has committed to conduct a study in patients with moderately impaired hepatic function.

Erlotinib and its metabolites are not significantly excreted by the kidney, as less than 9 % of a single dose is excreted in the urine. In population pharmacokinetic analysis, no clinically significant relationship was observed between erlotinib clearance and creatinine clearance. The safety and efficacy of erlotinib has not been studied in patients with renal impairment (serum creatinine concentration >1.5 times the upper normal limit). Based on pharmacokinetic data no dose adjustments appear necessary in patients with mild or moderate renal impairment. There are no available data for patients with a creatinine clearance <15 ml/min and use of Tarceva in patients with severe renal impairment is not recommended. Adequate information has been provided in sections 4.2 and 5.2 of the SPC.

The safety and efficacy of erlotinib has not been studied in patients under the age of 18 years. Use of Tarceva in paediatric patients is not recommended (see SPC section 4.2).

Erlotinib is a potent inhibitor of CYP1A1, and a moderate inhibitor of CYP3A4 and CYP2C8, as well as a strong inhibitor of glucuronidation by UGT1A1 *in vitro*. The physiological relevance of the strong inhibition of CYP1A1 is unknown due to the very limited expression of CYP1A1 in human tissues.

The inhibition of glucuronidation may cause interactions with medicinal products which are substrates of UGT1A1 and exclusively cleared by this pathway. Patients with low expression levels of UGT1A1 or genetic glucuronidation disorders (e.g. Gilbert's disease) may exhibit increased serum concentrations of bilirubin and must be treated with caution, and this has been adequately refelected in the SPC (see section 4.5). Based on the clinical safety data, the risk of severe hyperbilirubinemia is considered to be small.

Since erlotinib is metabolised, primarily by CYP3A4 and to a lesser extent by CYP1A2, potent inducers of CYP3A4 may reduce the efficacy of erlotinib whereas potent inhibitors of CYP3A4 may lead to increased toxicity. Concomitant treatment with these types of agents should be avoided (see SPC section 4.5). Reduced exposure has been observed for the potent CYP3A4 inducer rifampicin, and may also occur with other inducers e.g. phenytoin, carbamazepine, barbiturates or St. Johns Wort (*hypericum perforatum*). Caution should be observed when these drugs are combined with erlotinib. Alternate treatments lacking potent CYP3A4 inducing activity should be considered when possible. Caution should be used when erlotinib is combined with a potent CYP3A4 inhibitor, e.g. azole antifungals (i.e. ketoconazole, itraconazole, voriconazole), protease inhibitors, erythromycin or clarithromycin. If necessary the dose of erlotinib should be reduced, particularly if toxicity is observed. No clinical interaction study with a CYP3A4 substrate has been performed. Based on *in vitro* data, combination of erlotinib with CYP3A4 substrates should be conducted with caution. If such a combination is considered necessary a close clinical monitoring should be performed. In a clinical study, erlotinib was shown not to affect pharmacokinetics of the concomitantly administered CYP3A4/2C8 substrate paclitaxel. About 30% of the in-vitro metabolism of erlotinib is attributed to CYP1A2 activity. A pharmacokinetic interaction study to investigate this aspect was not considered necessary taking into consideration the relatively small numbers of drugs that are strong inhibitors of

CYP1A2 and the small likelihood that these would be prescribed concomitantly with erlotinib. Adequate warnings are provided in the SPC to highlight that the effects of CYP1A2 inhibitors on the pharmacokinetic of erlotinib have not been investigated and caution should be observed when these inhibitors are combined with erlotinib (see SPC section 4.5). Cigarette smoking is known to induce hepatic CYP1A2 via activation of the aryl hydrocarbon (Ah) receptor [39, 40]. Based on the results of the population pharmacokinetic study, patients who are still smoking should be encouraged to stop smoking while taking Tarceva, as plasma concentrations could be reduced otherwise (see SPC section 4.5). The applicant committed to submit for evaluation the final report for a clinical interaction study for evaluating the effect of smoking on erlotinib pharmacokinetics.

Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung, and CYP1B1 in tumour tissue also potentially contribute to the metabolic clearance of erlotinib. Since erlotinib is found to be a strong mechanism-based inhibitor of CYP1A1, the overall contribution of lung metabolism by CYP1A1 is expected to be negligible. CYP1B1 might contribute to erlotinib clearance especially after induction by smoking [32]. The substrate specificity of CYP1B1 as a drug-metabolizing enzyme has not been investigated. Potential interactions may occur with drugs which are metabolised by, or are inhibitors or inducers of, these enzymes. Adequate information has been included in the SPC (see section 4.5). The applicant has committed to study this effect in the ongoing PK study in smokers.

Co-administration of cytochrome P450 inhibitors or inducers was not associated with changes in erlotinib CL in the population pharmacokinetic analysis but detailed documentation were lacking. Furthermore, the drug interactions between erlotinib and CYP3A4 inhibitors or inducers might be less profound at steady state than the interaction after administration of a single dose of erlotinib with the most potent CYP3A4 inhibitor or inducers.

International Normalized Ratio (INR) elevations, and bleeding events including gastrointestinal bleeding have been reported in clinical studies, some associated with concomitant warfarin administration (see section 4.8) and some with concomitant NSAID administration. Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR. A clinical interaction study with midazolam as probe-drug to measure effects of erlotinib on CYP3A4 substrates has been initiated.

No apparent interaction was found while studying the influence of a number of chemotherapy agents (cisplatin, carboplatin, gemcitabine, paclitaxel, docetaxel, or capecitabine). However, these latter observations have their origin from studies that were not specifically designed to detect an interaction which should be kept in mind. The applicant is conducting the pharmacokinetics phase I studies investigating the pharmacokinetic interactions of erlotinib and docetaxel, capecitabine, or paclitaxel/carboplatin.

In vitro studies does not suggest that erlotinib has a significant potential of clinical relevant inhibition or induction on the metabolism of other drugs.

Discussion on dosing

The dose selection is reasonably well justified based on a rather clear dose response relationship from in vitro and mice xenograph models and human MTD studies.

The applicant conducted an exploratory analysis to investigate the relationship between measures of erlotinib exposure and various efficacy and safety outcomes in Study BR.21 (data not shown). A PK/PD relation in patients has not been established.

The possibility of recommending individualised dosing has been explored. The observation of an association between severity and frequency of rash and efficacy of treatment has been made early in the development of erlotinib, and a confirmation of this finding was also seen in the erlotinib arm of BR.21. In the 363 erlotinib-treated patients who developed rash, the median survival was 9.49 months (95% CI: 7.95 – 10.91), and it was 2.22 months (95% CI: 1.71 – 2.76) for the 122 erlotinib-treated patients with no rash. However, no landmark analysis was conducted and the confounding effects due to the time-dependent nature of both rash and survival are acknowledged. Furthermore, there was a relatively high degree of rash in the placebo arm of study BR.21, and even in the placebo arm, the absence of a rash indicated a poorer outcome. The interim-results of a PKPD study to determine the feasibility of intrapatient dose escalation to tolerable rash in pretreated patients with NSCLC do not suggest a higher response rate in patients undergoing dose escalation[41]. It may also be possible that current smokers with a suggested induction of erlotinib drug clearance derive a benefit from dose

escalation. The applicant committed to investigate the feasibility and safety for a controlled dose-increase in patients with an increased erlotinib clearance due to smoking. In conclusion there are currently insufficient data on these phenomena to enable individualized dosing, but data from ongoing and future trials will help to address this question.

Clinical efficacy

The clinical development program of erlotinib in NSCLC as single-agent treatment of locally advanced or metastatic Stage IIIB/ IV non-small cell lung cancer after failure of at least one prior chemotherapy regimen consisted of the pivotal study BR.21 and the supportive Phase II study A248-1007.

- Main studies

Title

A randomized placebo-controlled study of OSI-774 (Tarceva) in patients with incurable stage IIIB/IV Non-Small Cell Lung Cancer who have failed standard therapy for advanced metatsatic disease (protocol No. BR.21) [20].

METHODS

Study Participants

This was a multinational randomised, double-blind, placebo-controlled study of erlotinib conducted in 731 patients with incurable stage IIIB/IV NSCLC after failure of at least 1 prior chemotherapy regimen. Patients were randomised across 86 centers in 17 countries. The first patient was randomised in November 2001 and the last patient in January 2003 with lock of database in April 2004. The study was initiated and conducted under the sponsorship of the NCIC CTG in Canada and of OSI for the international sites.

Patients were stratified at enrollment by center, number of prior regimens (one vs. two), prior platinum therapy (yes vs. no), best response to prior therapy (CR or PR vs. SD vs. PD), and Eastern Cooperative Oncology Group (ECOG) performance status (PS) and randomised 2:1 to receive erlotinib 150 mg tablets orally or placebo once daily. Treatment continued daily until disease progression or unacceptable toxicity.

The main selection criteria included histologically or cytologically confirmed diagnosis of incurable stage IIIB/IV non-small cell carcinoma of the lung; patients had to have evidence of disease but measurable disease was not mandatory; 18 years of age or older; with the exception of elderly patients (≥70 years), all patients must have received at least 1 combination chemotherapy regimen and must not be planned to receive further palliative cytotoxic chemotherapy. No more than 2 prior chemotherapy regimens were allowed. Elderly patients may have received 1 or 2 prior single agent regimens for their disease. Patients must have recovered from any toxic effects and at least 21 days must have elapsed from the last dose and prior to randomisation; Patients may have received prior radiation therapy providing that they have recovered from any toxic effects thereof and at least 7 days have elapsed between the last fraction and randomisation; ECOG performance status of 0, 1, 2 or 3; Adequate renal and hepatic function defined by the following laboratory values within 7 days prior to randomisation (serum creatinine < 1,5 times the UNL, total bilirubin < 1,5 UNL, ALT < 2 times the UNL). Patients with any of the following conditions were not eligible: significant history of cardiac disease; serious active infection or other serious underlying medical conditions that would impair the ability of the patient to receive protocol treatment; known CNS metastases unless asymptomatic and on a stable dose of corticosteroids; any condition that does not permit compliance with the protocol; pregnant or lactating; patients with clinically significant ophthalmologic or gastrointstinal abnormalities.

Treatments

Patients were randomised 2:1 to receive erlotinib 150 mg tablets orally or placebo once daily. Treatment continued daily until disease progression or unacceptable toxicity. Treatment had to be given within 2 working days from randomisation. No dose escalation of erlotinib/placebo was permitted and study drug was reduced for toxicities based on NCI-CTC criteria in steps of 50 mg. Study drug was given at a fixed dose of 150 mg as a single daily oral dose preferably in the morning. The drug was supposed to be taken at least 1 hour before or 2 hours after the ingestion of any food or

other medications, including grapefruit juice, vitamins and iron supplements. Treatment was administered on an outpatient basis.

Objectives

The primary objective was to compare overall survival between the 2 arms in patients with incurable stage IIIB/IV NSCLC who have failed standard therapy for advanced disease. Secondary objectives were to compare quality of life, progression-free survival (PFS), response rates (RR), to estimate response duration, toxicity, to correlate the expression of tissue EGFR levels (at diagnosis) with outcomes and response to treatment, to measure and correlate trough levels of erlotinib with clinical responses and/or adverse events

Outcomes/endpoints

The primary efficacy endpoint according to study protocol was overall survival defined as the time from randomisation until death from any cause. The secondary efficacy endpoints included quality of life of patients assessed using EORTC QLQC30 [42] and the lung cancer module (QLQ LC13) [43]. The questionnaire was completed at baseline, every 4 weeks on therapy, and at the 4- and 12-week post-treatment follow-up visits. Progression free survival (PFS) was defined as the time from randomisation to the first observation of disease progression or death due to any cause. A patient who stopped treatment with study drug and went on receiving alternative therapy for NSCLC, prior to documentation of disease progression, was censored on the date alternative therapy began. Objective tumour response was assessed for patients with at least one measurable leason at baseline and at least one disease assessment after baseline using RECIST criteria. Assessments were done every six weeks for the first 24 weeks and every 12 weeks thereafter. Duration of response (PR/CR) was defined as the time from first objective status assessment of CR/PR to the first time disease progression is documented or death. For the first 330 patients tumour responses or progression were assessed by an independent radiologist. The remaining 401 patients were assessed by the investigators only. Patients were assessed 4 weeks after discontinuing protocol treatment and then followed every 12 weeks until death.

Sample size

According to a revised sample size calculation, a total of 582 events were required to detect a 33% (initially 50%) improvement in median survival (hazard ratio .75, initially .67) with erlotinib, using a two-sided 5% level test of significance and 90% power, assuming a median survival of 4 months for the placebo arm. With an expected accrual time of 14 months and 6 months additional follow-up before final analysis, a sample size of 700 patients was calculated.

Randomisation

Randomisation was stratified by centre, ECOG performance status (0 + 1 vs 2 + 3), best response to prior treatment (CR or PR vs. SD vs. PD), number of prior regimens (1 vs 2), exposure to platinum (yes vs. no) using a dynamic minimisation technique.

Blinding (masking)

Each dosage strength of erlotinib and placebo tablets was manufactured to be indistinguishable from each other in appearance, smell, and taste. The study was double-blind, neither the investigator nor the patient was supposed to have knowledge about the assigned treatment.

Statistical methods

All randomised patients were included in the intent-to-treat (ITT) primary analysis of overall survival. The 2 treatment arms were compared using the stratified log-rank test by stratification factors at randomisation (see above) and EGFR expression status (positive vs negative vs unknown). No interim analysis was planned.

The primary endpoint in the QoL analysis was time from baseline assessment to deterioration in the following QoL symptoms: cough, dyspnea, and pain. Patients were considered as deteriorated for a given symptom if their change in score from the baseline on the domain/single item defining this symptom was 10 points or higher, on a 1 – 100 scale, at any time-point after the baseline assessment. For each symptom, all patients who had a baseline and at least 1 of the follow-up QoL assessments were included in the time to deterioration analysis. Patients were censored at the time of the last QoL questionnaire completion if they had not deteriorated before that. The time to deterioration in each

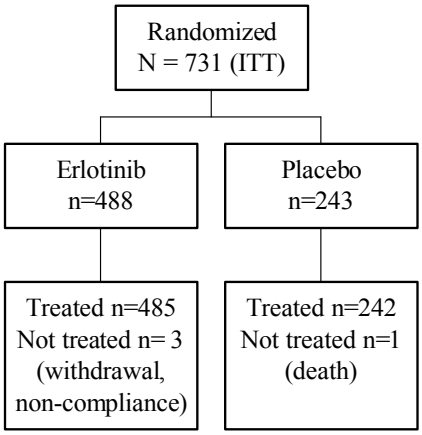
symptom was compared between the 2 treatment arms using unstratified log-rank tests, and the Hochberg procedure was used to adjust the obtained p-values for multiple comparisons.

RESULTS

Participant flow

In total, 731 patients were randomised (Figure 1). The majority of the treatment discontinuations were because of PD or symptomatic progression: 64% and 8% in the erlotinib arm 75% and 8% in the placebo arm, respectively. The deaths listed (12% erlotinib arm and 9% placebo arm) were primarily because of PD or disease-related complications.

Figure 1. Participant flow



Recruitment

Accrual lasted from 1 November 2001 until 31 January 2003. The cut-off date for the study report submitted in the initial application (database lock) was 23 April 2004.

Conduct of the study

The protocol was amended 3 times, mainly to provide information about the possibility of drug interaction between erlotinib and warfarin, to change in the sample size from 330 to 700 patients, and to provide management and dose adjustment recommendations for interstitial pneumonitis.

Eligibility deviations as checked by NCIC CTG medical review were found in 2% of patients in the erlotinib arm and 4% of patients in the placebo arm. The most common deviation was the administration of 3 prior chemotherapies (a maximum of 2 was allowed). The applicant considered the potential impact of these deviations as negligible on the efficacy and safety results of the study. Other study conduct deviations (investigational therapeutic; Quality of Life; therapeutic modification) were noted in 1% of patients in the erlotinib arm and in 3% of patients in the placebo arm.

Baseline data

The main baseline characteristics are provided in table 4. The median time from most recent progression/relapse to randomisation was 0.5 months in both groups. EGFR expression at baseline were interpretable for 31% of the patients in the erlotinib arm and for 35% of the patients in the placebo arm. It is unknown how many of the samples were from the time of initial diagnosis or from a subsequent relapse. In the erlotinib arm, 16% of patients (representing 51% of the patients with known results) had a positive EGFR expression and 15% (49% of the patients with known results) had a negative expression, compared with 20% and 15% (representing 57% and 43% of patients with known results) in the placebo arm.

Table 4. Baseline Demographics and Disease Characteristics Part 1 Study BR.21

Characteristics		Erlotinib (N = 488)	Placebo (N = 243)
Gender No. (%)	Female	173 (35)	83 (34)
	Male	315 (65)	160 (66)
Race No. (%)	White	379 (78)	188 (77)
	Black	18 (4)	12 (5)
	Oriental	63 (13)	28 (12)
	Other	28 (6)	15 (6)
Age No. (%)	< 65	299 (61)	153 (63)
	≥ 65	189 (39)	90 (37)
Age (Years)	Median	62	59
	Range	34 - 86	32 - 88
Weight (kg)	Median	65	65
	Range	28 - 125	38 - 117
ECOG Performance Status No. (%)	0	64 (13)	34 (14)
	1	256 (52)	132 (54)
	2	126 (26)	56 (23)
	3	42 (9)	21 (9)
Weight Loss in Previous 6 Months No. (%)	< 5%	320 (66)	166 (68)
	5 - 10%	96 (20)	36 (15)
	> 10%	52 (11)	29 (12)
	Unknown	20 (4)	12 (5)
Smoking History No. (%)	Never smoked	104 (21)	42 (17)
	Current or Ex-smoker	358 (73)	187 (77)
	Unknown	26 (5)	14 (6)
Histological Classification No. (%)	Adenocarcinoma	246 (50)	119 (49)
	Squamous	144 (30)	78 (32)
	Undifferentiated Large Cell	41 (8)	23 (9)
	Mixed Non-Small Cell	11 (2)	2 (<1)
	Other	46 (9)	21 (9)
Time From Initial Diagnosis (Months) No. (%)	<6	63 (13)	34 (14)
	6 – 12	157 (32)	85 (35)
	>12	268 (55)	124 (51)
Number of prior regimens No. (%)	1	243 (50)	121 (50)
	2	238 (49)	119 (49)
	3	7 (1)	3 (1)
Previous Therapy No. (%)	Chemotherapy	488 (100)	243 (100)
	Surgery	487 (100)	242 (100)
	Radiation	264 (54)	143 (59)
	Hormonal Therapy	1 (<1)	1 (<1)
	Other Prior Therapy	2 (<1)	2 (<1)
Prior Taxane Therapy No. (%)	No	311 (64)	153 (63)
	Yes	177 (36)	90 (37)
Time From Initial Diagnosis to Randomization (Months)	Median	13.1	12.2

Numbers analysed

All 731 patients were included in the ITT efficacy analyses and description of baseline characteristics; 4 patients did not start protocol treatment and were excluded from the safety analyses.

Outcomes and estimation

At the time of final analysis 587 deaths had occurred and 144 patients were still alive or lost to follow-up: 110 patients (23%) in the erlotinib arm and 34 patients (14%) in the placebo arm.

Overall survival

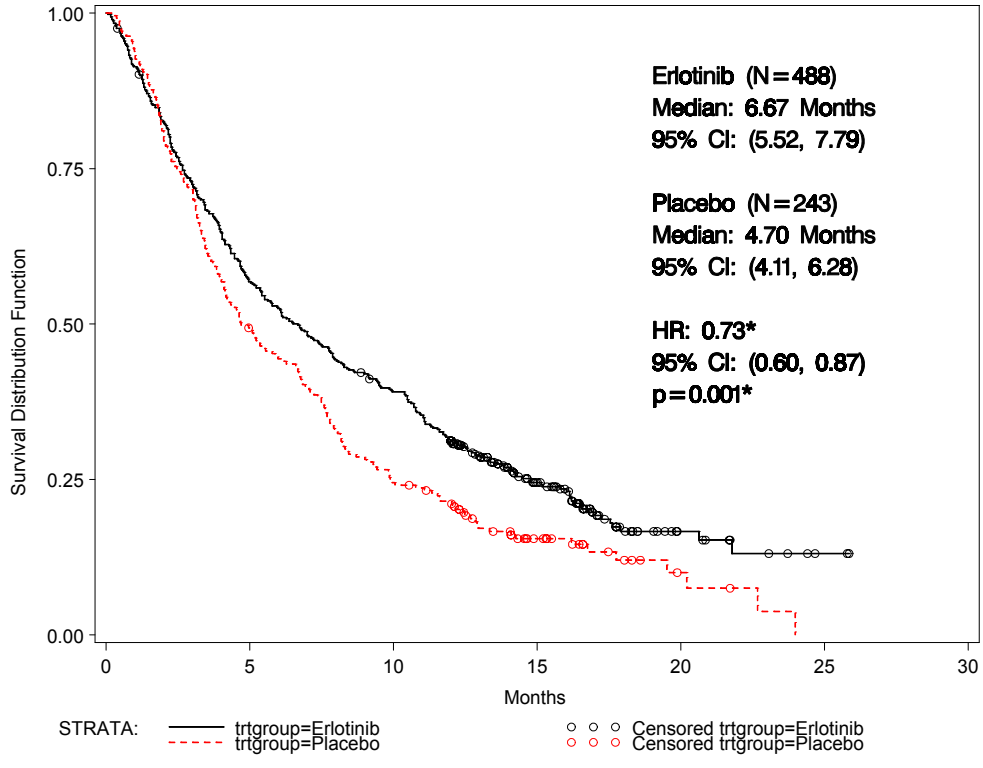
The main efficacy results of study BR.21 are summarised in table 5. The median overall survival was 6.67 months in the erlotinib arm (95% CI, 5.52 – 7.79 months) *v.* 4.70 months in the placebo arm (95% CI, 4.11 – 6.28 months). The actuarial 12-month survival rates were 31.2% and 21.5%, respectively. The Kaplan-Meier curve for overall survival in Study BR.21 is shown in figure 2. The HR for death in the erlotinib arm relative to the placebo arm estimated from the primary analysis (adjusted for stratification factors at randomization and EGFR expression status) was 0.73 (95% CI, 0.60 – 0.87) (P = .001).

Table 5. Study BR.21 efficacy results

	Tarceva N = 488	Placebo N = 243	p-value
Median survival 95 % CI	6.7 months (5.5 - 7.8)	4.7 months (4.1 - 6.3)	
Difference between survival curves			0.001
Hazard Ratio* (Erlotinib : Placebo) 95 % CI	0.73 0.60 - 0.87		0.001
Median time to deterioration in cough*** 95 % CI	28.1 weeks (16.1 - 40.0)	15.7 weeks (9.3 - 24.3)	0.041**
Median time to deterioration in dyspnoea*** 95 % CI	20.4 weeks (16.3 - 28.3)	12.1 weeks (9.3 - 20.9)	0.031**
Median time to deterioration in pain*** 95 % CI	12.1 weeks (10.1 - 14.1)	8.1 weeks (7.7 - 12.3)	0.040**
Median progression-free survival 95 % CI	9.7 weeks (8.4 - 12.4)	8.0 weeks (7.9 - 8.1)	<0.001

* Adjusted for stratification factors and HER1/EGFR status; a value less than 1.00 favors Tarceva (primary analysis)
** p-value adjusted for multiple testing
*** From the EORTC QLQ-C30 and QLQ-LC13 quality of life questionnaires

Figure 2. Overall Survival of Patients by Treatment Group Study BR.21



*HR and p-value adjusted for stratification factors at randomization and EGFR expression status

Progression-Free Survival

The median PFS was 9.71 weeks in the erlotinib arm (95% CI, 8.43 –12.43 weeks) compared with 8.00 weeks in the placebo arm (95% CI, 7.86 – 8.14 weeks). The actuarial 26-week (6-month) PFS

rates were 24.5% and 9.3%, respectively, for the erlotinib and placebo arms. The primary analysis of PFS incorporated an adjustment for the same baseline factors used in the overall survival analysis (stratification factors and EGFR expression status). The adjusted HR for progression in the erlotinib arm relative to the placebo arm was 0.61 (95% CI, 0.51 – 0.73) ($p < 0.001$). In univariate analyses, the factors that were associated with worse PFS were: ECOG PS 2 or 3, and PD as best response to prior therapy. Neither the number of prior regimens nor exposure to prior platinum was predictive of PFS. EGFR status was marginally associated with PFS. Patients with EGFR-negative tumours had shorter PFS than patients with EGFR-positive tumours, the difference was not statistically different.

Objective response rate

The objective response rates in the erlotinib arm were 12/195 (6.2%) for the first 330 randomised patients and 26/232 (11.2%) for the last 401 randomised patients. A total of 4 CRs and 34 PRs were observed among the 427 patients with measurable disease treated with erlotinib, for an objective response rate of 8.9% (95% CI, 6.4 – 12.0%). An additional patient with only non-measurable lesions at baseline also achieved a CR while treated with erlotinib. Two responses were observed in the placebo arm (1 CR and 1 PR) for a 0.9% response rate. Both of these responses were in the group of 401 patients with less intense medical review. For patients with measurable disease, the median response duration was 34.3 weeks (95% CI, 24.71 – 46.29 weeks), ranging from 9.7 to 57.6+ weeks. Stable disease was observed in 35.1% of erlotinib-treated patients with measurable disease, compared with 26.5% of placebo-treated patients, for a CR + PR + SD rate of 44.0% and 27.5%, respectively. This difference was statistically significant, $p = 0.004$. Exploratory univariate analyses were performed to identify which baseline factors might predict response and response +SD with erlotinib. Response rates were higher among women (14.4%) than men (6.0%), higher among patients with adenocarcinomas (13.9%) than patients with squamous carcinomas (3.8%) or other histologies (4.5%), higher among patients who never smoked (24.7%) than current or ex-smokers (3.9%), and higher among patients with EGRF-positive tumours (11.6%) than patients with EGRF-negative tumours (3.2%).

A survival benefit of Tarceva was also observed in patients who did not achieve an objective tumour response (by RECIST). This was evidenced by a hazard ratio for death of 0.82 among patients whose best response was stable disease or progressive disease.

- Clinical studies in special populations

Clinical studies in patients with renal and/or hepatic impaiment have not been performed. Renal- or hepatic impairment have been exclusion criteria in the pivotal study BR.21. There have been no specific studies in elderly patients.

- Supportive study(ies)

Study A248-1007 was a single arm, open-label, multicenter Phase II trial to assess the efficacy and safety of erlotinib in patients with Stage IIIB or IV, EGFR-positive NSCLC after failure of prior platinum-based chemotherapy [19, 44, 45]. Patients received erlotinib, 150 mg daily until disease progression or unmanageable toxicity. Serial measurements of all disease sites were performed every 8 weeks and response and PFS were assessed by the investigators using WHO criteria and RECIST. No central evaluation was performed. Efficacy was further evaluated by periodic assessments of survival and health-related quality of life (HQoL).

The study population involved patients ≥ 18 years of age. The main criteria for inclusion were documented Stage IIIB or IV advanced or recurrent metastatic NSCLC, disease progression or relapse following platinum-based therapy, and confirmation of EGFR-positivity (based on immunohistochemical staining of the original tumour specimen, newly biopsied material, or cytospin of pleural fluid). Additional criteria included written informed consent; ECOG PS of 0 to 2; and adequate bone marrow, hepatic and renal function as defined by protocol criteria. Response rate was the primary efficacy endpoint in this study.

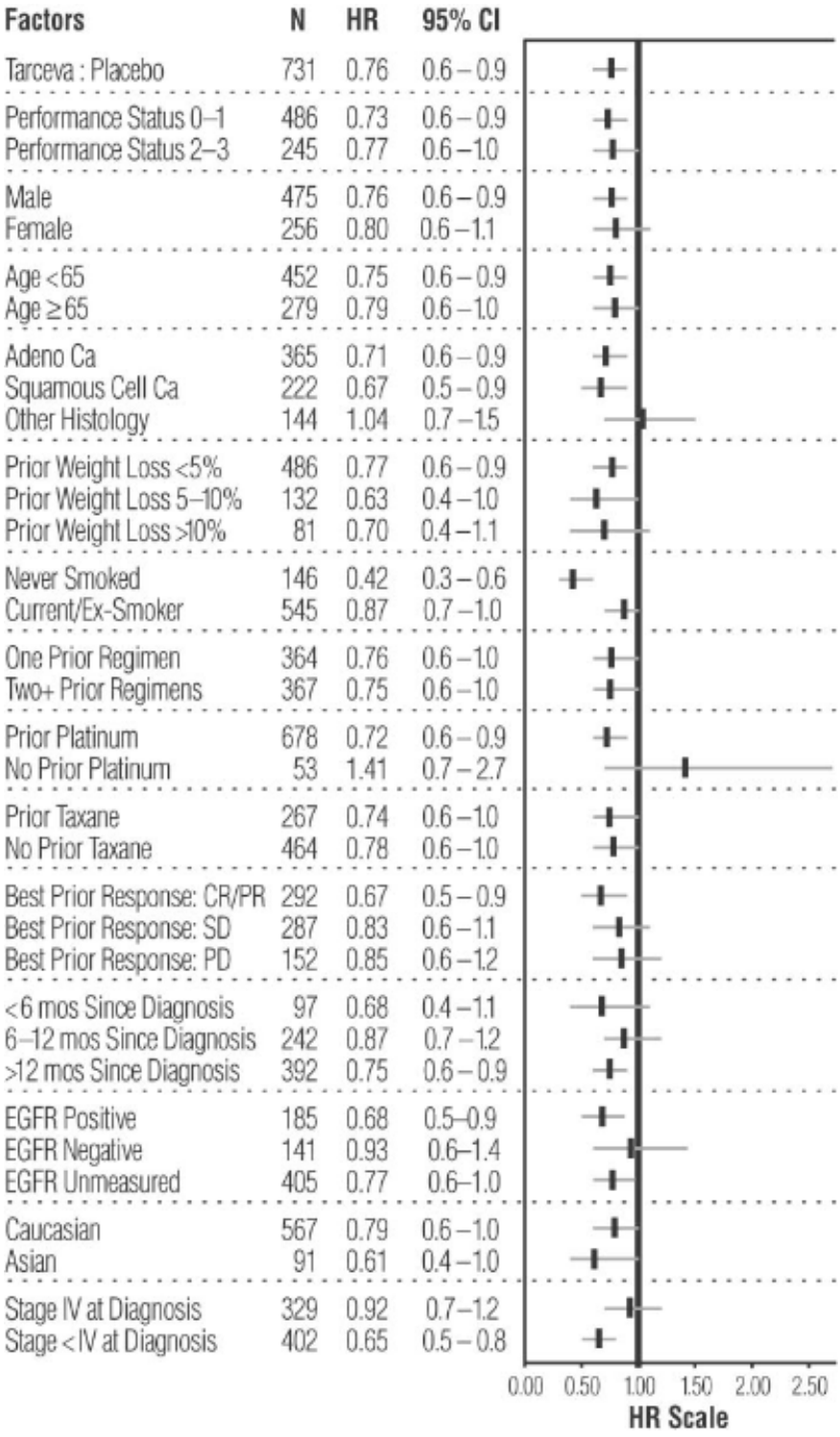
The 57 patients who entered the study represented a population with advanced NSCLC after failure of multiple prior chemotherapy regimens (median: 2 regimens, range: 1 – 8). Sixty percent of the patients were female. The median age was 62 years (range: 31 – 83). Most patients (77%) had an ECOG PS of 1, and the majority were ex-smokers (74%). The most common tumor type was adenocarcinoma (61%). The median time from initial diagnosis to study entry was 18 months (range:

4 – 137). All tumors were EGFR-positive. Of the 57 patients, 2 achieved a CR and 5 had a best response of PR as determined by both WHO and RECIST, for an objective response rate of 12.3% (95% CI, 5.1 – 23.7%). Twenty-two patients had SD (38.6%) and 28 patients (49.1%) had progressive disease (PD). The median duration of response was 19.7 weeks (range: 11.7 – 80.3). Response rates were similar regardless of type of prior chemotherapy or whether the patient had received 1, 2, or more prior regimens. With 9 patients still alive and censored in the analysis, the median overall survival was 8.4 months (95% CI, 4.8 – 13.9 months). The 1-year survival rate was 40.4% (95% CI, 27.6 – 54.2%). With 5 patients censored in the analysis, the median PFS was 9.0 weeks (95% CI, 8.0 – 15.3 weeks).

- Ancillary analyses

In an attempt to identify patient groups who are more likely to benefit from the treatment, the applicant conducted subgroup analyses for overall survival (figure 3). Regarding EGFR-expression status the applicant obtained tumour samples from additional 104 patients and EGFR results available for 326 patients (45% of all participants) of study BR.21. The updated results are presented in table 6. Updated curves for overall survival of EGFR-negative patients are shown in figure 4. Multivariate analyses were conducted to explore the existence of a treatment by EGFR status interaction. No statistically significant interaction was found in these exploratory analyses.

Figure 3. Hazard Ratio for Survival by Pretreatment Characteristics Study BR.21



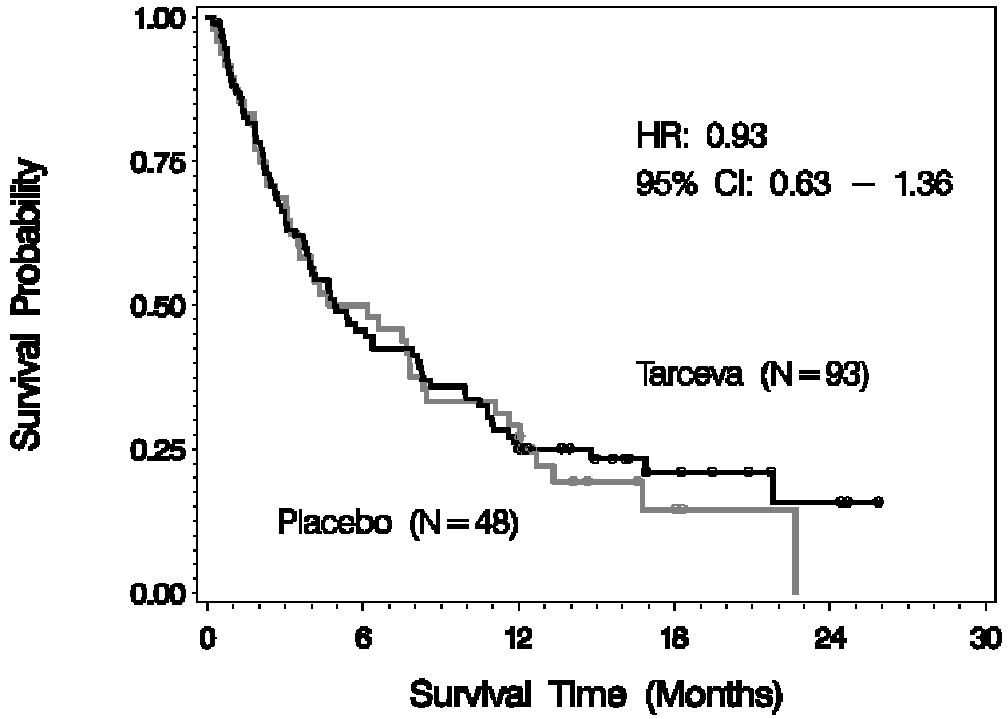
Note: Univariate hazard ratios (HR) for death in the Tarceva patients relative to the placebo patients, the 95 % confidence interval (CI) for the HR and the sample size in each subgroup are shown. The hash mark on the horizontal bar represents the HR, and the length of the horizontal bar represents the 95 % CI. A hash mark to the left of the vertical line corresponds to a HR that is less than 1.00, which indicates that survival is better in the Tarceva arm compared with the placebo arm in that subgroup.

Table 6. Overall Survival by EGFR Status

	Erlotinib		Placebo		Hazard Ratio	95% CI	p-value
Survival – stratified Log-Rank (Original)					0.73	(0.61, 0.86)	<0.001[a]
Survival – stratified Log-Rank (Updated)					0.74	(0.61, 0.89)	0.001[a]
Survival	**N**	**Median**	**N**	**Median**			
EGFR positive (Original)	78	10.7 mo	49	3.8 mo	0.65	(0.43, 0.97)	0.033[b]
EGFR positive (Updated)	117	8.6 mo	68	3.7 mo	0.68	(0.49, 0.94)	0.020[b]
EGFR negative (Original)	74	5.2 mo	37	7.5 mo	1.01	(0.65, 1.57)	0.958[b]
EGFR negative (Updated)	93	5.0 mo	48	5.4 mo	0.93	(0.63, 1.36)	0.696[b]
EGFR unknown (Original)	336	6.0 mo	157	5.1 mo	0.76	(0.61, 0.93)	0.008[b]
EGFR unknown (Updated)	278	6.3 mo	127	5.5 mo	0.77	(0.61, 0.98)	0.031[b]

a. Two-sided, stratified Log-Rank test, adjusted for stratification factors and EGFR status
b. Two-sided, univariate Log-Rank test, unadjusted for multiple comparisons

Figure 4. Survival in EGFR-Negative Patients – Updated EGFR Data



An analysis of outcome and EGFR mutation status (mutated *v.* wild-type) was attempted. EGFR mutation status was known for only 117/731 (16%) of patients of BR.21. No association was found between mutation status and outcome.

A higher proportion of patients receiving erlotinib received transfusions (7.8% vs. 4.5%). The summary of new concomitant medications begun during the study showed there were several medications and classes of medications taken more frequently by patients in the erlotinib group (e.g. anti-bacterials, corticosteroids). Twice as many patients received systemic antibiotics in the erlotinib

group (56% compared to 28%). A total of 29/488 (5.9%) of erlotinib patients received radiotherapy (33 treatments), compared to 26/243 (7.8%) of placebo patients (26 treatments).

- Discussion on clinical efficacy

The efficacy of erlotinib 150 mg daily monotherapy has been demonstrated compared to placebo in terms of overall survival in the claimed indication, based on the single phase III trial submitted. Concerning secondary endpoints such as objective response rate, progression-free survival and quality of life, the high prevalence of rash in the erlotinib arm combined with the 2:1 randomisation in favour of erlotinib raises doubts about the effectiveness of the blinding. Furthermore, no central radiology review was carried out for the majority of patients (n=401), and this raises questions about the claimed overall objective response rate and progression-free survival.

Currently, docetaxel and pemetrexed have been approved for 2nd-line treatment of NSCLC and their efficacy has been established according to current regulatory requirements. In view of the significant treatment effect in terms of overall survival observed for erlotinib compared to placebo, inferiority compared to single-agent docetaxel or pemetrexed seems unlikely and a randomised controlled study is not a requirement for the purpose of marketing authorisation. Nevertheless, the applicant has planned to conduct a phase III trial in patients with advanced NSCLC (stage IIIB /IV) who had progressive disease during 4 cycles of standard platinum based chemo-therapy (trial BO18602).

There are concerns about potential lack of efficacy in EGFR-negative patients. For a compound targeting EGFR signalling, solid evidence should be presented showing that the compound is active in EGFR-negative tumours (defined by IHC using the DAKO kit and defining positive as < 10% tumor cells staining). It is acknowledged that no statistically significant interaction of treatment by EGFR-status was observed in multivariate analysis, but the study has not been designed to ensure adequate power to detect such interactions. A hazard ratio of 1.01 (original) or 0.93 (updated) rather indicates lack of a meaningful effect, and the updated results regarding progression-free survival and tumour response (data not shown) did not provide useful information to establish efficacy in this subgroup of EGFR-negative patients show that the benefit of treatment is at best is moderate or not existing in this subgroup. This issue is further discussed with reference to the proposed therapeutic indication for Tarceva (see benefit risk assessment).

Tarceva resulted in symptom benefits by significantly prolonging time to deterioration in cough dyspnoea and pain, versus placebo. These symptom benefits were not due to an increased use of palliative radiotherapy or concomitant medications in the Tarceva group. It is reassuring that treatment with erlotinib slightly improved QoL regarding cough, dyspnoea and pain and that the toxicities of treatment (diarrhoea, sore mouth) did not impair the overall quality of life compared to placebo. A general improvement of the quality of life cannot be concluded from the data.

The applicant has committed to submit for evaluation a report investigating the reason for the imbalance in antibiotic treatment (e.g. with tetracyclines, penicillins with a broad spectrum, other aminoglycosides and lincosamides). Also, the applicant has committed to submit for evaluation a report supporting and informing of the number of surgeries/procedures/resuscitations and other non-drug related treatments that might have had an impact on survival.

Further studies are ongoing or planned, such as trials to test the influence of CYP3A4 activity on erlotinib pharmacokinetics (NP17536), erlotinib MTD with concurrent administration of pemetrexed (BP18193), erlotinib pharmacokinetics in smokers and non-smokers (OSI 774-103), in hepatically-impaired patients (OSI 774-104) and in rifampicin-exposed healthy volunteers (OSI 774-105).

The applicant is conducting two studies in patients with NSCLC that aim to identify prognostic markers such as tumoral EGFR-expression status and EGFR mutations and analyze interrelationships with clinical efficacy parameters. The prospective studying of the correlation between tumoural EGFR mutation status and clinical outcome is of great relevance. An adjuvant phase III study in patients with NSCLC Ib-IIIA after 4 cycles of platinum-based chemotherapy will also assess tumoral EGFR-expression status. Blood samples will be collected to determine the EGFR polymorphisms. The relationships between EGFR polymorphism to survival and PFS will be analyzed, as well as the correlation between EGFR polymorphism and other markers (e.g. EGFR mutation, EGFR expression).

Clinical safety

The primary safety population was defined as the 759 patients treated with at least one 150 mg dose of Tarceva monotherapy during Phase III study BR.21, Phase II study A248-1007, and three Phase II studies in populations other than NSCLC: 248-101 (ovarian cancer), A248-1003 (head and neck cancer), and OSI2288g (metastatic breast cancer) and the 242 patients who received placebo in study BR.21.

- Patient exposure

Duration of treatment is summarised in table 7. Relative dose intensity, expressed as the proportion of the total intended dose (ie, 150 mg daily) over the entire treatment period versus the dosing that was actually received, is summarized in table 8.

Table 7. Duration of Treatment

	BR.21 Placebo (N=242)		BR.21 Erlotinib (N=485)		A248-1007 (N=57)		Erlotinib Phase II (N=217)	
Weeks of Treatment	**< 150 mg**	**150 mg**	**< 150 mg**	**150 mg**	**< 150 mg**	**150 mg**	**< 150 mg**	**150 mg**
Median	2.8	8.0	12.0	8.1	6.5	9.1	4.9	6.7
Range	2 - 9	1 - 65	0 - 68	0 - 111	5 - 8	2 - 131	0 – 53	1 - 93

Notes: Phase II Studies = A248-101, A248-1003, OSI2288g. Patients may appear in both the < 150 mg and 150 mg columns.

Table 8. Relative Dose Intensity

	BR.21 Placebo (N=242)		BR.21 Erlotinib (N=485)		A248-1007 (N=57)		Erlotinib Phase II (N=217)	
	n	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
> 90%	226	(93)	376	(78)	55	(96)	155	(71)
80-90%	7	(3)	23	(5)	1	(2)	17	(8)
< 80%	9	(4)	86	(18)	1	(2)	45	(21)

Notes: Phase II Studies = A248-101, A248-1003, OSI2288g. Relative dosing intensity was calculated by dividing the total reported doses by the number of treatment days (last treatment day - first treatment day +1), divided by expected total dose.

- Adverse events

Adverse events regardless of causality occurring more frequently (≥ 3%) in the erlotinib group than in the placebo group in Study BR.21 are summarized in the table 9. by decreasing frequency in the BR.21 erlotinib group. The term "RASH," was created by pooling similar preferred MedDRA terms.

Table 9. Incidence of Patients with Adverse Events – BR.21 Erlotinib Arm ≥ 3% higher than Placebo Arm

	BR.21 Placebo (N=242)			BR.21 Erlotinib (N=485)			A248-1007 (N=57)			Erlotinib Phase II (N=217)		
Grade	**Any**	**3**	**4**	**Any**	**3**	**4**	**Any**	**3**	**4**	**Any**	**3**	**4**
MedDRA Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Total patients with any AE	233 (96)	87 (36)	54 (22)	481 (99)	195 (40)	107 (22)	57 (100)	19 (33)	18 (32)	216 (100)	85 (39)	49 (23)
RASH	42 (17)	0 (0)	0 (0)	366 (75)	40 (8)	3 (<1)	47 (82)	1 (2)	0 (0)	185 (85)	22 (10)	2 (<1)
Diarrhoea	44 (18)	2 (<1)	0 (0)	261 (54)	28 (6)	1 (<1)	32 (56)	1 (2)	0 (0)	110 (51)	12 (6)	0 (0)
Anorexia	93 (38)	11 (5)	1 (<1)	250 (52)	38 (8)	5 (1)	7 (12)	0 (0)	0 (0)	43 (20)	1 (<1)	0 (0)
Fatigue	108 (45)	39 (16)	10 (4)	250 (52)	67 (14)	19 (4)	27 (47)	3 (5)	0 (0)	91 (42)	12 (6)	3 (1)
Dyspnoea	84 (35)	36 (15)	27 (11)	198 (41)	82 (17)	52 (11)	19 (33)	7 (12)	2 (4)	48 (22)	12 (6)	6 (3)
Cough	70 (29)	6 (2)	0 (0)	159 (33)	18 (4)	0 (0)	23 (40)	2 (4)	0 (0)	37 (17)	2 (<1)	0 (0)
Nausea	59 (24)	4 (2)	0 (0)	158 (33)	14 (3)	0 (0)	22 (39)	1 (2)	0 (0)	85 (39)	15 (7)	1 (<1)
Infection	37 (15)	5 (2)	0 (0)	116 (24)	20 (4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)
Vomiting	47 (19)	4 (2)	0 (0)	113 (23)	9 (2)	2 (<1)	13 (23)	1 (2)	0 (0)	60 (28)	12 (6)	1 (<1)

	BR.21 Placebo (N=242)			BR.21 Erlotinib (N=485)			A248-1007 (N=57)			Erlotinib Phase II (N=217)		
Grade	**Any**	**3**	**4**	**Any**	**3**	**4**	**Any**	**3**	**4**	**Any**	**3**	**4**
MedDRA Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Stomatitis	8 (3)	0 (0)	0 (0)	83 (17)	4 (<1)	0 (0)	2 (4)	0 (0)	0 (0)	17 (8)	1 (<1)	1 (<1)
Pruritus	12 (5)	0 (0)	0 (0)	61 (13)	2 (<1)	0 (0)	20 (35)	2 (4)	0 (0)	41 (19)	4 (2)	0 (0)
Dry skin	9 (4)	0 (0)	0 (0)	60 (12)	0 (0)	0 (0)	20 (35)	1 (2)	0 (0)	67 (31)	2 (<1)	0 (0)
Conjunctivitis	5 (2)	1 (<1)	0 (0)	57 (12)	3 (<1)	0 (0)	2 (4)	0 (0)	0 (0)	8 (4)	1 (<1)	0 (0)
Keratoconjunctivitis sicca	8 (3)	0 (0)	0 (0)	56 (12)	0 (0)	0 (0)	3 (5)	0 (0)	0 (0)	28 (13)	0 (0)	0 (0)
Abdominal pain	17 (7)	3 (1)	1 (<1)	52 (11)	10 (2)	1 (<1)	4 (7)	1 (2)	0 (0)	20 (9)	5 (2)	1 (<1)
Insomnia	12 (5)	1 (<1)	0 (0)	44 (9)	2 (<1)	0 (0)	13 (23)	2 (4)	0 (0)	27 (12)	0 (0)	0 (0)
Epistaxis	2 (<1)	0 (0)	0 (0)	34 (7)	0 (0)	0 (0)	3 (5)	0 (0)	0 (0)	19 (9)	0 (0)	0 (0)
Alopecia	2 (<1)	0 (0)	0 (0)	26 (5)	0 (0)	0 (0)	3 (5)	0 (0)	0 (0)	13 (6)	0 (0)	0 (0)
Nail disorder	1 (<1)	0 (0)	0 (0)	20 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	0 (0)	0 (0)
Palmar-plantar erythrodysaesthesia syndrome	0 (0)	0 (0)	0 (0)	17 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	0 (0)	0 (0)

Studies with Healthy Volunteers

Adverse events have also been assessed in 279 healthy volunteers in studies during which subjects had limited exposure to erlotinib or placebo. As with cancer patients, the most common adverse events among healthy volunteers exposed to erlotinib were rash and diarrhea. The diarrhea was mostly considered mild in severity and reversible, however, the rash as considered moderately severe in some healthy subjects dosed for up to 7 days and lasted for almost up to 1 year. The occurrence of these adverse effects, most notably acneiform rash, limited the ability of some healthy volunteers to complete the protocol-specified dosing regimens. Erlotinib 200 mg orally twice daily repetitive dosing evaluated in Study 248-002 was not well tolerated by healthy male subjects. This study produced the first evidence of severe rash characterized by the investigator as an erythematous rash or a follicular exanthema. The rashes developed on the face, neck, chest, and back of all 6 subjects who received erlotinib 200 mg twice daily 3 to 4 days after the first dose. Dosing was discontinued after 4 to 5 days and the study was terminated.

Phase III study OSI2298g

This was a phase III randomised double blind multicenter trial of erlotinib plus chemotherapy (Carboplatin and Paclitaxel) versus chemotherapy alone (carboplatin and paclitaxel) in patients with advanced NSCLC. 1079 patients were enrolled. The erlotinib arm had a higher incidence of study drug-related serious adverse events relative to the placebo arm (8.6% erlotinib, 2.4% placebo). The most common events included diarrhea (3.8% erlotinib, 1.1% placebo) and rash (dermatitis acneiform) (0.8% erlotinib, 0% placebo). There were also a greater number of patients with serious adverse events that were attributed by the investigator as leading to death in the erlotinib arm. Such events were experienced by 53 of 526 patients in the erlotinib arm (10.1%) and 27 of 533 patients in the placebo arm (5.1%). The majority of these events (63 of 80) occurred in the first 4 months of study participation (43 erlotinib; 20 placebo).

Phase III study BO16411

This was a phase III, randomised, double-blind, multicenter trial of erlotinib plus chemotherapy (Cisplatin and Gemcitabine) versus chemotherapy alone in patients with advanced NSCLC. 1172 patients were enrolled. Overall, gastrointestinal disorders were the most frequently-reported events, and occurred more frequently in the erlotinib group (75% vs. 69% in the placebo group). There was a marked elevation in the incidence of diarrhea in the erlotinib group (40% vs. 17% in the placebo group). The most notable imbalance between the groups related to the incidence of skin disorders (70% vs 34%) arising minly from rash (66% vs. 19%). Other body systems in which there was a higher incidence of events on active treatment were metabolism and nutrition disorders (38% vs. 33%: mainly driven by anorexia and dehydration), investigations (28% vs 21%, mainly driven by weight decrease), renal and urinary disorders (13% vs. 7%: mainly renal failure) and eye disorders (9% vs. 5%: mainly conjunctivitis). Overall, there was a higher incidence of NCI-CTC grade 3 and 4 events in the erlotinib group (77%) than in the placebo group (72%). The proportion of deaths was similar between the treatment groups (48% of patients dying due to PD in the erlotinib group vs 46% in the

placebo group; 11% dying due to AE in the erlotinib group vs. 12% in the placebo group). Almost all events leading to death were considered by the investigators as unrelated to study medication, but there was an increased incidence of events considered as probably related to study medication in the erlotinib group. Some events only resulted in death for patients in the erlotinib group. Notable amongst these are renal failure and acute renal failure, from which four patients died, febrile neutropenia, neuropenic sepsis and neutropenia, from which four patients died and diarrhea, from which two patients died. The incidence of serious adverse events was higher in the erlotinib group (53%) than in the placebo group (47%). This was driven by an excess of serious events in the erlotinib group in four body systems: blood and lymphatic system disorders (mainly anemia and thrombocytopenia), gastrointestinal disorders (mainly diarrhea), renal and urinary disorders, and skin and subcutaneous tissue disorders. There was a marked increase in the incidence of serious renal disorders in the erlotinib group relative to the placebo group (17 patients, 3% vs. 5 patients, <1%). Renal failure and acute renal failure were the major events behind this, recorded in 12 erlotinib patients but in only 2 placebo patients.

- Serious adverse event/deaths/other significant events

Serious adverse events and deaths

The incidence of serious adverse events in Study BR.21 was slightly higher in the erlotinib arm than in the placebo arm (34% versus 28%), which was lower than the incidences in Study A248-1007 (47%) and the combined Phase II studies (40%). The most common serious adverse events that occurred at least twice as often in the erlotinib arm as in the placebo arm of Study BR.21 include fatigue, pneumonia, dehydration, diarrhea, and vomiting. Across all study populations, the most common serious adverse events were respiratory disorders and the rates were consistent and balanced in the controlled study (BR.21, 16% versus 14% in placebo; A248-1007, 28%; other Phase II, 11%. In Study BR.21, serious gastrointestinal adverse events were more frequent (≥ 5%) in the erlotinib arm than in the placebo arm (10% versus 3%), as were infections and infestations (8% versus 3%). This is consistent with the incidences observed in A248-1007 and the other Phase II studies, in which 7% and 11%, respectively, experienced gastrointestinal disorders and 14% and 9%, respectively, experienced Infection and Infestation disorders. More patients in the erlotinib arm of Study BR.21 (8%) experienced treatment-related serious adverse events than in the placebo arm (3%). Treatment-related serious metabolism and nutrition disorders were also slightly more common in the erlotinib arm (3%) than in the placebo arm (< 1%). Excluding NSCLC as the primary cause of death, 5% of patients in the erlotinib group of Study BR.21, 4% in the placebo group, and 5% in Study A248-1007 died of other causes. Death was attributed to toxicity from protocol treatment in 2 erlotinib-treated patients and 1 placebo-treated patient in Study BR.21. In addition, 2 other erlotinib-treated patients died from a combination of NSCLC and protocol treatment complications. No patients died from treatment-related adverse events in Study A248-1007 or in the Phase II studies. In general, serious adverse events were most often associated with the underlying NSCLC, with dyspnea being the most commonly occurring serious adverse event. The incidence of serious adverse events in Study BR.21 was slightly higher in the erlotinib arm than in the placebo arm (34% versus 28%), which was lower than the incidences in Study A248-1007 (47%) and the combined Phase II studies (40%). Across all study populations, the most common serious adverse events were respiratory disorders and the rates were consistent and well balanced in the controlled study (BR.21, 16% versus 14% in placebo; A248-1007, 28%; other Phase II, 11%. In Study BR.21, serious gastrointestinal adverse events were more frequent (≥ 5%) in the erlotinib arm than in the placebo arm (10% versus 3%), as were infections and infestations (8% versus 3%). This is consistent with the incidences observed in A248-1007 and the other Phase II studies, in which 7% and 11%, respectively, experienced gastrointestinal disorders and 14% and 9%, respectively, experienced Infection and Infestation disorders. More patients in the erlotinib arm of Study BR.21 (8%) experienced treatment-related serious adverse events than in the placebo arm (3%). Treatment-related serious metabolism and nutrition disorders were also slightly more common in the erlotinib arm (3%) than in the placebo arm (< 1%). In Study A248-1007, serious adverse events considered treatment-related were reported in 2 patients (4%), including 1 patient who experienced Grade 2 nausea and vomiting and 1 patient with Grade 2 cellulitis. There was no Grade 3 or 4 treatment-related serious adverse event reported during Study A248-1007. Treatment-related serious adverse events were reported in 5% of the patients in the combined Phase II studies. These were all single episodes of mainly gastrointestinal disorders (diarrhea, pancreatitis, dysphagia) and general disorders (fatigue, pyrexia, edema). Deaths In Study BR.21, 32% of the erlotinib group and

29% of the placebo group died during treatment or within 30 days of the last dose, as did 35% of patients in Study A248-1007. For most patients, the primary cause of death within 30 days of last dose was attributed by the Investigators to be NSCLC (ie, progressive disease): 27% in the BR.21 erlotinib-treated group versus 26% in the placebo group and 30% in Study A248-1007. Excluding NSCLC as the primary cause of death, 5% of patients in the erlotinib group of Study BR.21, 4% in the placebo group, and 5% in Study A248-1007 died of other causes. Death was attributed to toxicity from protocol treatment in 2 erlotinib-treated patients and 1 placebo-treated patient in Study BR.21. In addition, 2 other erlotinib-treated patients died from a combination of NSCLC and protocol treatment complications (see the following table). No patients died from treatment-related adverse events in Study A248-1007 or in the Phase II studies. In the Japanese Phase I study (JO16564), 2 of the 15 patients died within 30 days of last dose of study drug: 1 patient due to progressive disease and 1 patient due to interstitial pneumonia attributed to erlotinib therapy by the Investigator, although this diagnosis was not confirmed by autopsy findings.

Targeted Adverse Events

Adverse events that had a notable higher incidence in the BR.21 erlotinib arm when compared with the placebo arm orthat were considere of special interest included: skin and subcutaneous tissue disorders (78% versus 24%), gastrointestinal disorders (74% versus 50%), respiratory, thoracic and mediastinal disorders (66% versus 62%), infections and infestations (32% versus 20%), eye disorders (27% versus 9%), and metabolism and nutritional disorders (55% versus 41%).

- Skin and Subcutaneous Tissue Disorders

In Study BR.21, the median time to onset of rash was approximately 1 week (8 days compared with 18 days in the placebo group). The prevalence of rash by study period (i.e., 4 weeks) suggests that the rate remains fairly constant in patients who stay on study drug. The rash appears to diminish following discontinuation based on the prevalence observed during the second follow-up visit. The severity of rash was mainly Grade 1 or 2 during the on-study period and mainly Grade 1 during follow-up. The incidence of RASH observed in patients receiving single-agent erlotinib is consistent with that observed in the studies of erlotinib with concurrent chemotherapy. In Study OSI2298g the composite incidence of RASH was 81% and 43% in the erlotinib and placebo groups, respectively, and 66% and 19%, respectively, in Study BO16411.

- Gastrointestinal Disorders

The overall incidence of gastrointestinal disorders was 74% in the erlotinib arm of Study BR.21 (50% in the placebo arm), 88% in Study A248-1007, and 84% in the combined Phase II studies. Slightly over half of erlotinib-treated patients experienced diarrhea (54% in BR.21 erlotinib arm, 56% in Study A248-1007, and 51% in the combined Phase II studies). Diarrhea was generally of mild or moderate severity, although 6% of patients in the BR.21 erlotinib arm experienced Grade 3 diarrhea, as did 6% of patients in the combined Phase II studies and 1 patient in Study A248-1007. The median time to first diarrhea was 12 days and 19 days in the erlotinib group and placebo group, respectively, of Study BR.21. The prevalence by study period remained fairly constant but significantly decreased during the follow-up periods, suggesting reversibility of diarrhea upon study drug cessation.

- Respiratory, Thoracic and Mediastinal Disorders

Cases of interstitial lung disease (ILD), including fatalities, have been reported uncommonly in patients receiving Tarceva for treatment of non-small cell lung cancer (NSCLC) or other advanced solid tumours. In the pivotal study BR.21 in NSCLC, the incidence of ILD (0.8 %) was the same in both the placebo and Tarceva groups. The overall incidence in Tarceva-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.6 % compared to 0.2 % in patients on placebo. Reported diagnoses in patients suspected of having ILD included pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome (ARDS), and lung infiltration. Confounding or contributing factors such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections were frequent.

- Infections and Infestations

There was a higher incidence of infections and infestations in the BR.21 erlotinib arm than in the placebo arm (32% versus 20%). The incidence was 46% in study A248-1007 and 31% in the

combined Phase II studies. In Study BR.21, 8% of erlotinib-treated patients and 3% of placebo-treated patients experienced infections as a serious adverse event. In 2 of the erlotinib-treated patients, the serious adverse event was considered treatment related (pneumonia and hepatitis B). The apparent higher rate of pulmonary infections in the erlotinib arm of study BR.21 was no longer evident when adjusted for the longer survival experienced by this group.

- Ophthalmological Disorders

Eye disorders occurred in 27% of patients in the BR.21 erlotinib arm (9% in the placebo group), 19% of patients in A248-1007, and 32% in the combined Phase II studies. These events were predominately of mild or moderate severity, with Grade 3 or 4 events reported in 5 patients (1%) of the BR.21 erlotinib arm, 1 patient in Study A248-1007, and 3 patients (1%) in the combined Phase II studies. Three of the 5 patients in the BR.21 erlotinib arm who had eye disorders experienced Grade 3/4 conjunctivitis, as did 1 patient in the combined Phase II studies. No other type of Grade 3 or 4 eye disorder was reported in more than 1 erlotinib-treated patient.

One isolated case of corneal ulceration was reported in one patient receiving Tarceva with concurrent chemotherapy, as a complication of mucocutaneous inflammation.

- Metabolism and Nutrition Disorders

The overall incidence of metabolism and nutrition disorders was higher in the erlotinib arm than in the placebo arm of Study BR.21 (55% versus 41%), primarily due to the difference in the incidence of anorexia: 52% versus 38%.

- Bleeding Disorders

In Study BR.21, 10 patients (2%) in the erlotinib arm had a gastrointestinal hemorrhage compared with 1 patient (< 1%) in the placebo arm. Eight of these were serious adverse events, 5 of which were considered treatment related. All 8 serious cases were associated with contributing factors that included concomitant warfarin administration in 2 patients, concurrent NSAID in 3 patients, and anti-ulcer medication in 4 patients suggesting active peptic ulcer disease. Overall, 24% of patients in the erlotinib arm and 17% of patients in the placebo arm experienced a bleeding disorder. Hemoptysis was most frequent but balanced between the 2 treatment arms (15% versus 14%), followed by epistaxis, which was more frequent in erlotinib-treated patients (7% versus < 1%). Most events were of Grade 1 severity. To correct for the longer survival time observed in the erlotinib arm, the incidence of serious bleeding per patient weeks was calculated. The rate in the erlotinib arm was 7.64 per patient weeks compared with 18.22 in the placebo arm.

Laboratory findings

The worst CTC grades for selected laboratory parameters regarding hematology and biochemistry are shown in table 10.

Table 10 Summary of Worst CTC Grade for Selected Laboratory Parameters

	BR.21 Placebo (N = 242)			**BR.21 Erlotinib (N = 485)**			**A248-1007 (N = 57)**			**Erlotinib Phase II (N = 217)**		
Grade	**Any**	**3**	**4**	**Any**	**3**	**4**	**Any**	**3**	**4**	**Any**	**3**	**4**
	n (%)	**(%)**	**(%)**	**n (%)**	**(%)**	**(%)**	**n (%)**	**(%)**	**(%)**	**n (%)**	**(%)**	**(%)**
Total Hemoglobin	208 (86)	(2)	(0)	419 (86)	(2)	(<1)	57 (100)	(2)	(0)	215 (99)	(2)	(<1)
WBC	208 (86)	(0)	(0)	419 (86)	(0)	(0)	57 (100)	(0)	(0)	215 (99)	(0)	(0)
Platelet Count	208 (86)	(0)	(0)	418 (86)	(<1)	(<1)	57 (100)	(0)	(0)	215 (99)	(0)	(0)
Neutrophils	185 (76)	(0)	(0)	374 (77)	(<1)	(0)	57 (100)	(0)	(0)	215 (99)	(0)	(<1)
Serum Creatinine	203 (84)	(0)	(0)	409 (84)	(0)	(0)	57 (100)	(0)	(0)	215 (99)	(<1)	(<1)
Total Bilirubin	202 (83)	(0)	(0)	407 (84)	(<1)	(0)	57 (100)	(0)	(0)	214 (99)	(<1)	(0)
ALT/SGPT	204 (84)	(<1)	(0)	402 (83)	(0)	(0)	56 (98)	(0)	(0)	214 (99)	(4)	(<1)
AST/SGOT	8 (3)	(<1)	(0)	26 (5)	(0)	(0)	57 (100)	(2)	(0)	214 (99)	(5)	(<1)

- Safety in special populations

The overall incidence of adverse events was similar in males and females and in patients < 65 years of age and those ≥ 65. In Study BR.21, the incidence of adverse events was, in general, higher in Caucasians compared with Asians even in the placebo group. In the erlotinib arm of Study BR.21, there was a notably higher incidence of gastrointestinal disorders among patients with performance status 0 or 1 than among patients with performance status 2 or 3 (83% versus 56%). The difference in the incidence of gastrointestinal disorders among patients with performance status 0 or 1 than among patients with performance status 2 or 3in the erlotinib arm of Study BR.21 included diarrhea (62% versus 39%), nausea (36% versus 25%), and vomiting (25% versus 20%). The incidence of RASH among patients with performance status 0 or 1 was 82% compared with 63% among patients with performance status 2 or 3 in the erlotinib arm of Study BR.21. This incidence of 63% among patients with performance status 2 or 3 is notably less than the overall incidence of RASH among erlotinib-treated patients (75%).

No clinical studies in patients with hepatic impairment have been completed. The influence of hepatic metastases and/or hepatic dysfunction on the pharmacokinetics of erlotinib is not currently known. Liver function test abnormalities (including increased alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). These were mainly mild or moderate in severity, transient in nature or associated with liver metastases.

No clinical studies have been conducted or are planned in patients with compromised renal function.

- Safety related to drug-drug interactions and other interactions

Interaction with Anticoagulants: Phase II and Phase III studies included increased surveillance of coagulation parameters (INR). Systematic data collection was only performed in Study BR.21 in patients receiving concurrent warfarin. On-study INR values were available for 32 erlotinib-treated patients and 14 placebo-treated patients. Shifts to values that may be associated with significant bleeding risks (INR ≥ 4) were seen in 11 erlotinib-treated patients (27%) and 4 placebo-treated patients (21%). Approximately half in each arm developed shifts to INR of > 6, which may be associated with greatest risk of bleeding episodes. None of these patients, however, experienced serious clinical bleeding.

Interaction with CYP3A4 Inhibitors: The incidence of dose reductions or discontinuations was similar between those patients who received CYP3A4 inhibitors and those who did not (data not shown).

- Discontinuation due to adverse events

In study BR.21, adverse events led to study drug discontinuation in 4 (2%) *v.* 25 (5%, with diarrhoea 1%, and rash 1%) patients, for placebo and erlotibib, respectively, and to dose reduction in 0 (0%) *v.* 42 (9%, with rash 6%, and diarrhoea 1%) patients, for placebo and erlotinib, respectively.

- Post marketing experience

No post marketing experience was available at the time of submission of the application.

Discussion on clinical safety

Compared to other chemotherapies, based on the current clinical safety database, erlotinib has a favourable safety profile when used as a single-agent. The observed adverse events have been in accordance with the findings of the preclinical studies.

Rash (75 %) and diarrhoea (54 %) were the most commonly reported adverse drug reactions (ADRs). Most were Grade 1/2 in severity and manageable without intervention. Grade 3/4 rash and diarrhoea occurred in 9 % and 6 %, respectively in Tarceva-treated patients and each resulted in study discontinuation in 1 % of patients. Dose reduction for rash and diarrhoea was needed in 6 % and 1 % of patients, respectively. In study BR.21, the median time to onset of rash was 8 days, and the median time to onset of diarrhoea was 12 days.

Skin-related AEs are very frequent with erlotinib and appear within the first month of drug treatment in the majority of cases. Erlotinib-associated facial rush was the most common form of skin toxicity and was reversible upon withdrawal of erlotinib. Erlotinib-associated skin toxicity thus very closely resembles skin toxicity as known from gefitinib.

Diarrhoea has occurred in approximately 50% of patients on Tarceva and moderate or severe diarrhoea should be treated with e.g. loperamide. In some cases dose reduction may be necessary. In the clinical studies doses were reduced by 50 mg steps. Dose reductions by 25 mg steps have not been investigated. In the event of severe or persistent diarrhoea, nausea, anorexia, or vomiting associated with dehydration, Tarceva therapy should be interrupted and appropriate measures should be taken to treat the dehydration (see section 4.8).

The tablets contain lactose and should not be administered to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption (see SPC section 4.4).

There was a consistent and high incidence of usually mild and dose-related skin and gastrointestinal AEs, that resulted in study discontinuation in 1% of erlotinib-treated patients (BR.21). No clear association has been found between erlotinib administration and cardiac disorders, bleeding disorders, laboratory abnormalities and infections. Dry eyes were more frequent in erlotinib-exposed patients (4%) as opposed to placebo-exposed patients (1%). In conclusion, adverse events associated with erlotinib treatment are reasonably well defined, and the most common adverse events, i.e. gastrointestinal disturbances and skin rash, are mostly mild and reversible upon dose reductions or drug withdrawal.

Overall, 34% of patients in the erlotinib arm of study BR.21 developed a serious adverse event as compared to 28% in the placebo arm. The most common serious adverse events that occurred at least twice as often in the erlotinib arm as in the placebo arm of Study BR.21 included fatigue, pneumonia, dehydration, diarrhea, and vomiting. These serious adverse events were not unexpected and the absolute increase of 6% in the treatment group is moderate compared to many other chemotherapies. An increase of treatment related deaths has not been observed in studies investigating single-drug treatment with erlotinib, although in combination treatment serious adverse events that were attributed by the investigator as leading to death in the erlotinib arm were higher compared to placebo. The generally favourable safety profile is also reflected by the small number of patients discontinuing treatment due to adverse events.

In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms such as dyspnoea, cough and fever, Tarceva therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, Tarceva should be discontinued and appropriate treatment initiated as necessary (see section 4.8).

There are no studies in pregnant women using erlotinib but studies in animals have shown some reproductive toxicity (see Toxicology). The potential risk for humans is unknown. Women of childbearing potential must be advised to avoid pregnancy while on Tarceva. Adequate contraceptive methods should be used during therapy, and for at least 2 weeks after completing therapy. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the foetus. It is not known whether erlotinib is excreted in human milk. Because of the potential harm to the infant, mothers should be advised against breastfeeding while receiving Tarceva. This information is adequately reflected in the SPC (see section 4.6), and package leaflet.

Single oral doses of Tarceva up to 1000 mg erlotinib in healthy subjects, and up to 1600 mg in cancer patients have been tolerated. Repeated twice daily doses of 200 mg in healthy subjects were poorly tolerated after only a few days of dosing. Based on the data from these studies, severe adverse events such as diarrhoea, rash and possibly increased activity of liver aminotransferases may occur above the recommended dose of 150 mg. In case of suspected overdose, Tarceva should be withheld and symptomatic treatment initiated (this is reflected in the SPC, see section 4.8).

No studies on the effects on the ability to drive and use machines have been performed; however erlotinib is not associated with impairment of mental ability (this is reflected in the SPC, see section 4.7).

Patient groups at higher risk of adverse drug reactions have not been identified. The impact of slight to moderate liver impairment on safety has not been investigated. The applicant has committed to submit for evaluation the final study report for the planned pharmacokinetic study in cancer patients with hepatic dysfunction once the study is finalised.

5 Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way

Non-clinical pharmacology and toxicology

Erlotinib is an epidermal growth factor receptor/ human epidermal growth factor receptor type 1 (EGFR also known as HER1) tyrosine kinase inhibitor. Erlotinib potently inhibits the intracellular phosphorylation of EGFR. EGFR is expressed on the cell surface of normal cells and cancer cells. In non-clinical models, inhibition of EGFR phosphotyrosine results in cell stasis and/or death.

Chronic dosing effects observed in at least one animal species or study included effects on the cornea (atrophy, ulceration), skin (follicular degeneration and inflammation, redness, and alopecia), ovary (atrophy), liver (liver necrosis), kidney (renal papillary necrosis and tubular dilatation), and gastrointestinal tract (delayed gastric emptying and diarrhoea). Red blood cell parameters were decreased and white blood cells, primarily neutrophils, were increased. There were treatment-related increases in ALT, AST and bilirubin. These findings were observed at exposures well below clinically relevant exposures.

Based on the mode of action of the compound, Erlotinib, has the potential to be a teratogen. Data from reproductive toxicology tests in rats and rabbits at doses near the maximum tolerated dose and/or maternally toxic doses showed reproductive (embryotoxicity in rats, embryo resorption and foetotoxicity in rabbits) and developmental (decrease in pup growth and survival in rats) toxicity, but was not teratogenic and did not impair fertility. These findings were observed at clinically relevant exposures.

Erlotinib tested negative in conventional genotoxicity studies. Carcinogenicity studies have not been performed.

A mild phototoxic skin reaction was observed in rats after UV irradiation.

Efficacy

The efficacy and safety of Tarceva was demonstrated in a randomised, double-blind, placebo-controlled trial (BR.21), in 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen. Patients were randomised 2:1 to receive Tarceva 150 mg or placebo orally once daily. Study endpoints included overall survival, progression-free survival (PFS), response rate, duration of response, time to deterioration of lung cancer-related symptoms (cough, dyspnoea and pain), and safety. The primary end-point was survival.

Demographic characteristics were well balanced between the two treatment groups. About two-thirds of the patients were male and approximately one-third had a baseline ECOG performance status (PS) of 2, and 9 % had a baseline ECOG PS of 3. Ninety-three percent and 92 % of all patients in the Tarceva and placebo groups, respectively, had received a prior platinum-containing regimen and 36 % and 37 % of all patients, respectively, had received a prior taxane therapy.

The adjusted hazard ratio (HR) for death in the Tarceva group relative to the placebo group was 0.73 (95 % CI, 0.60 to 0.87) (p = 0.001). The percent of patients alive at 12 months was 31.2 % and 21.5 %, for the Tarceva and placebo groups respectively. The median overall survival was 6.7 months in the Tarceva group (95 % CI, 5.5 to 7.8 months) compared with 4.7 months in the placebo group (95 % CI, 4.1 to 6.3 months).

The effect on overall survival was explored across different patient subsets. The effect of Tarceva on overall survival was similar in patients with a baseline performance status (ECOG) of 2-3 (HR = 0.77, CI 0.6-1.0) or 0-1 (HR = 0.73, 0.6-0.9), male ((HR = 0.76, CI 0.6-0.9) or female patients (HR = 0.80, CI 0.6-1.1), patients < 65 years of age (HR = 0.75, CI 0.6-0.9) or older patients (HR = 0.79, CI 0.6-1.0), patients with one prior regimen (HR = 0.76, CI 0.6-1.0) or more than one prior regimens (HR = 0.75, CI 0.6-1.0), Caucasian (HR = 0.79, CI 0.6-1.0) or Asian patients (HR = 0.61, 0.4-1.0), patients with adenocarcinoma (HR = 0.71, CI 0.6-0.9) or squamous cell carcinoma (HR = 0.67, CI 0.5-0.9), but not in patients with other histologies (HR 1.04, CI 0.7-1.5), patients with stage IV disease at diagnosis (HR = 0.92, CI 0.7-1.2) or < stage IV disease at diagnosis (HR = 0.65, 0.5-0.8).

Patients who never smoked had a much greater benefit from erlotinib (survival HR = 0.42, CI 0.28-0.64) compared with current or ex-smokers (HR = 0.87, CI 0.71-1.05).

In the 45 % of patients with known EGFR-expression status, the hazard ratio was 0.68 (CI 0.49-0.94) for patients with EGFR-positive tumours and 0.93 (CI 0.63-1.36) for patients with EGFR-negative tumours (defined by IHC using EGFR pharmDx kit and defining EGFR-negative as less than 10% tumour cells staining). In the remaining 55 % of patients with unknown EGFR-expression status, the hazard ratio was 0.77 (CI 0.61-0.98).

The median PFS was 9.7 weeks in the Tarceva group (95 % CI, 8.4 to 12.4 weeks) compared with 8.0 weeks in the placebo group (95 % CI, 7.9 to 8.1 weeks).

The objective response rate by RECIST in the Tarceva group was 8.9 % (95 % CI, 6.4 to 12.0 %). The first 330 patients were centrally assessed (response rate 6.2 %); 401 patients were investigator-assessed (response rate 11.2 %). The median duration of response was 34.3 weeks, ranging from 9.7 to 57.6+ weeks. The proportion of patients who experienced complete response, partial response or stable disease was 44.0 % and 27.5 %, respectively, for the Tarceva and placebo groups (p = 0.004). A survival benefit of Tarceva was also observed in patients who did not achieve an objective tumour response (by RECIST). This was evidenced by a hazard ratio for death of 0.82 (95% CI, 0.68 to 0.99) among patients whose best response was stable disease or progressive disease.

Tarceva resulted in symptom benefits by significantly prolonging time to deterioration in cough dyspnoea and pain, versus placebo.

Safety

Rash (75 %) and diarrhoea (54 %) were the most commonly reported adverse drug reactions (ADRs). Most were Grade 1/2 in severity and manageable without intervention. Grade 3/4 rash and diarrhoea occurred in 9 % and 6 %, respectively in Tarceva-treated patients and each resulted in study discontinuation in 1 % of patients. Dose reduction for rash and diarrhoea was needed in 6 and 1 % of patients, respectively. In study BR.21, the median time to onset of rash was 8 days, and the median time to onset of diarrhoea was 12 days.

No clear association has been found between erlotinib administration and cardiac disorders, bleeding disorders, laboratory abnormalities and infections. Dry eyes were more frequent in erlotinib-exposed patients (4%) as opposed to placebo-exposed patients (1%).

In conclusion, adverse events associated with erlotinib treatment are reasonably well defined, and the most common adverse events, i.e. gastrointestinal disturbances and skin rash, are mostly mild and reversible upon dose reductions or drug withdrawal.

Benefit/risk assessment

Based on the results submitted in this application, it can be concluded that erlotinib monotherapy has demonstrated antitumour activity and a significant overall survival benefit when compared with placebo in patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. These efficacy results represent a significant clinical effect in the second or third line treatment of an advanced stage of a disease. There are two common adverse events connected to erlotinib treatment, rash and diarrhoea but they were generally manageable and relatively few were characterised as severe or life-threatening. The generally favourable safety profile is also reflected by the small number of patients discontinuing treatment due to adverse events.

The CHMP consulted the Scientific Advisory Group (SAG) for oncology to provide guidance on whether it is possible to quantify the benefit of erlotinib in treatment of patients with EGFR negative tumours, and to what extent can the benefit in this patient population be considered clinically meaningful. The SAG commented that a compound targeting EGFR signalling would generally be expected to be less active, or inactive, in EGFR-negative tumours, compared to EGFR-positive ones. The BR.21 study included a heterogeneous population of both patients with EGFR-negative and EGFR-positive tumours, and varying treatment effects would be expected based on theoretical grounds. To test this hypothesis, unplanned subgroup analyses were conducted. The BR.21 study and the documentation presented failed to provide any formal or exploratory evidence suggesting a relevant treatment effect in EGFR-negative patients. Unfortunately, BR.21 was not powered to test for an interaction between treatment and EGFR expression, or to detect small treatment effects in EGFR-negative patients. Furthermore, the collection of material to allow determination of EGFR-expression

status and other markers was not systematic, and this further weakened the possibility to study different treatment effects across subgroups. These are considered pitfalls of the study, given the theoretic background. The SAG acknowledged that other factors, independent from EGFR status overexpression, might also be associated with response to erlotinib. It is also acknowledged that EGFR status may be subject to measurement error (false-positive and false-negative results, non-validated methods, arbitrary cut-off values for defining positive patients, etc.), and this adds to the difficulty of studying the association between EGFR-expression and response to erlotinib. Further data and a better understanding of the molecular mechanisms involved are needed in order to establish a potential benefit of erlotinib in EGFR-negative patients.

The SAG concluded that it is not possible to quantify the benefit (if any) of erlotinib in EGFR-negative patients, and there are no data or rationale to support the existence of a clinically meaningful effect in this subgroup. With respect to EGFR-status, a clinically relevant effect of erlotinib has only been demonstrated in EGFR-positive patients. EGFR-status should be known and taken into account together with all factors associated with response to treatment in order to allow a rational choice of treatment. There is no pharmacological rationale for using erlotinib in EGFR-negative patients.

Concerning exploratory evidence from BR.21, the observed response rate in this subgroup was low (3%), and there were no data to suggest an effect on overall survival or other meaningful endpoints in these patients. Whether erlotinib is associated with any clinically meaningful benefit in EGFR-negative patients is unknown, although the observed results and pharmacological rationale do not support this hypothesis. EGFR expression testing can be used in clinical practice. There is a need to improve on the methods that will make the determination more reliable but this is not considered to be a major hurdle by the SAG. Such approach has become the standard for trastuzumab treatment, which is only given to patients who are so-called 3+ in the Dako test or 2+ and 3+ in the FISH for Her2neu.

Having considered the advice from the SAG and the data and justifications presented by the applicant, the CHMP acknowledged that the discussion about the relation of EGFR receptor status/mutations and efficacy is ongoing, and that further data are needed to resolve the issue conclusively. There remains considerable uncertainty about the precise role of EGFR-expression and other independent factors and treatment effect (e.g., smoking history, gender, performance status, etc.). In view of the overall positive results of the trial and the need to take into account all positive and negative predictive factors, the CHMP supported a recommendation for a therapeutic indication, but with mentioning that no survival benefit or other clinically relevant effect of erlotinib has been observed in EGFR-negative patients (defined by IHC using EGFR pharmDx kit and defining EGFR-negative as less than 10% tumour cells staining), and that prescribing physicians should refer to the results of the subgroup analysis in section 5.1 for deciding what patients should receive treatment with Tarceva.

Tarceva treatment should be supervised by a physician experienced in the use of anticancer therapies.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the benefit/risk ratio of Tarceva indicated for: “the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. When prescribing Tarceva, factors associated with prolonged survival should be taken into account. No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR negative tumours (see section 5.1)” was favourable and therefore recommended the granting of the marketing authorisation.

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