Generic Name

Erlotinib 25 mg, 100 mg and 150 mg tablets

Brand Name

Tarceva

Manufacturer

OSI Pharmaceuticals

Summary

Erlotinib, being a Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase inhibitor, is indicated for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen. It has proven effective across most patient populations, regardless of prognostic factors. Co-treatment with the potent CYP3A4 inhibitor or inducers should be cautious.

Most common side effects associated with erlotinib are mild to moderate rash, diarrhea and pulmonary toxicity. Due to the fact that the drug is eliminated by hepatic metabolism and biliary excretion, it should be administered cautiously in patients with hepatic impairment. Use also with care in pregnancy.

Mechanism of Action

Erlotonib is a Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase inhibitor. It inhibits the intracellular phosphorylation of tyrosine kinase associated with the epidermal growth factor receptor, which is expressed on the cell surface of normal cells and cancer cells.

Pharmacokinetics

Absorption: Erlotinib is about 60% absorbed after oral administration, its bioavailability is substantially increased by food to almost 100% and peak plasma levels occur 4 hours after dosing. Its half-life is about 36 hours and it is cleared predominantly by CYP3A4 metabolism and to a lesser extent by CYP1A2.

Distribution: Following absorption, erlotinib is approximately 93% protein bound to albumin and alpha-1 acid glycoprotein and it has an apparent volume of distribution of 232 liters.

***Metabolism*:** Erlotinib is metabolized primarily by CYP3A4 and to a lesser extent by CYP1A2, and the extrahepatic isoform CYP1A1. Smokers had a

24% higher rate of erlotinib clearance. No data are currently available regarding the influence of hepatic dysfunction on the pharmacokinetics of erlotinib.

***Elimination*:** Following a 100 mg oral dose, 91% of the dose was recovered: 83% in feces and 8% in urine, predominantly in the form of metabolites. The half life is about 36 hours. No clinical studies have been conducted in patients with compromised renal function.

A population pharmacokinetic analysis in 591 patients receiving single-agent Tarceva® showed a median half-life of 36.2 hours. Time to reach steady state plasma concentration would therefore be 7 – 8 days. No significant relationships of clearance to covariates of patient age, body weight or gender were observed. Smokers had a 24% higher rate of Erlotinib clearance.

A second population pharmacokinetic analysis was conducted that incorporated Erlotinib data from 204 pancreatic cancer patients who received Erlotinib plus Gemcitabine. This analysis demonstrated that covariates affecting Erlotinib clearance in patients from the pancreatic study were very similar to those seen in the prior single-agent pharmacokinetic analysis. No new covariate effects were identified. Co-administration of Gemcitabine had no effect on Erlotinib plasma clearance.

Indication

Erlotinib monotherapy is 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.

Erlotinib in combination with gemcitabine is indicated for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

Similar Agents on Formulary

Gefitinib (as self-finance items)

Efficacy

On November 18, 2004, Tarceva tablets (erlotinib) received full approval as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. Approval was based on a single randomized, double-blind, multicenter, multinational trial in which orally administered Tarceva, 150 mg daily, was compared with placebo.

The trial was conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG).

A total of 731 patients were included in the study; 488 were randomly assigned to receive Tarceva and 243 patients, to receive placebo. The epidermal growth factor receptor (EGFR) status was determined for 238 (33%) of the 731 patients for whom tissue samples were available. Positive EGFR expression was defined as at least 10% of cells staining for the receptor with use of the EGFR pharmDx kit (Dako Cytomation, Carpinteria, California).

The primary efficacy objective was to compare overall survival between the two treatment arms. Secondary objectives were to compare progression-free survival; response rate and duration; and quality of life, as measured by the European Organization for the Research and Treatment of Cancer (EORTC) quality-of-life questionnaire QLQ-C30 and the lung cancer module QLQ-LC13. An additional objective was to correlate the EGFR expression in the tissue samples (at the time of diagnosis) with treatment outcome.

The two study arms were well balanced for sex, age, race, performance status before treatment, weight loss in the previous six months, smoking history (characterized as never smoked, current or ex-smoker, and unknown), histologic classification, time from initial diagnosis to randomization, best response to prior therapy, number of prior drug regimens, and prior platinum therapy. Of the 238 patients for whom tissue samples were available, 127 had positive EGFR expression (78 in the Tarceva arm and 49 in the placebo arm) and 111 had negative EGFR expression (74 in the Tarceva arm and 37 in the placebo arm).

Efficacy results are summarized in Table 1. Survival was significantly longer in the Tarceva arm than in the placebo arm.The adjusted hazard ratio (HR) for death in the Tarceva arm relative to the placebo arm was 0.73 ($p < 0.001$). Progression-free survival was significantly longer for patients in the Tarceva arm (*see Table 1 at end of article*). The adjusted HR was 0.59 ($p < 0.001$).

Objective response rate was also higher in the Tarceva arm (*see Table 1 at end of article*). The duration of response in the Tarceva arm ranged from 2.2 months to more than 13.3 months.

An exploratory analysis of EGFR expression status on the survival effect of treatment was performed. Tarceva prolonged survival for patients who had positive EGFR expression (HR = 0.65, $p = 0.033$) but had no apparent effect on survival for patients with negative EGFR expression (HR = 1.01, $p = 0.958$). However, the confidence intervals (CI) for the two subgroups are wide and overlap. Thus, a survival effect for Tarceva in the EGFR-negative subgroup cannot be excluded.

A subgroup analysis according to smoking status indicated that Tarceva was

associated with a greater survival benefit for patients who had never smoked (HR = 0.42; 95% CI, 0.3 to 0.6) than for smokers (HR = 0.87; 95% CI, 0.7 to 1.1).
A subgroup analysis according to EGFR expression status was also performed for patients who had never smoked. Among this group of patients, Tarceva led to a greater survival benefit for patients who had positive EGFR expression (HR = 0.27; 95% CI, 0.11 to 0.67; p = 0.003) than for those who had negative EGFR expression negative (HR = 1.4; 95% CI, 0.45 to 6.3; p = 0.58).
The quality-of-life analysis carried out by the sponsor was not found to be sufficiently robust or consistent to be included in the package insert.
In addition to trials involving patients with refractory disease, two large trials were conducted involving chemotherapy-naive patients with stage III and IV non-small cell lung cancer. In those studies, 2,251 patients were randomly assigned to receive Tarceva, 150 mg daily, or placebo in combination with platinum-based chemotherapy regimens. The chemotherapy regimens given in these trials of first-line therapy were gemcitabine and cisplatin (1,172 patients) or carboplatin and paclitaxel (1,079 patients). There was no evidence of benefit for Tarceva with respect to response rate, time to progression, or overall survival when compared with placebo.

Table 1. Efficacy of Tarceva Compared with Placebo

	Tarceva (n = 488)	Placebo (n = 243)	P Value
Overall survival	6.7 mos.	4.7 mos.	<0.001
Progression-free survival	9.9 wks.	7.9 wks.	<0.001
Objective response rate*	43 (8.8%) (95% CI, 6.4-12%)	2 (0.8%) (95% CI, 0.1-3.4%)	<0.001
Response duration All patients EGFR positive EGFR negative	 7.9 mos. 10.7 mos. 5.2 mos.	 3.7 mos. 3.8 mos. 7.5 mos.	

Results given as median.
*According to the Response Evaluation Criteria in Solid Tumors (RECIST).

To summarize, Tarceva was proven effective in diverse patient populations[18] Patients were not preselected to enrich the study population for favorable prognostic factors, ie, gender, smoking status or tumor histology. Tarceva was proven effective across most patient populations, regardless of prognostic factors.[18] Multivariate

analysis did not reveal a significant interaction between EGFR status and treatment outcome.A series of subsets of patients was examined in exploratory univariate analyses. The results of these analyses are shown in the chart.[18]

Drug Interactions

Co-treatment with the potent CYP3A4 inhibitor ketoconazole increases erlotinib AUC by 2/3. Caution should be used when administering or taking Tarceva® with ketoconazole and other strong CYP3A4 inhibitors such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), and voriconazole.

Pre-treatment with the CYP3A4 inducer rifampicin decreased Erlotinib AUC by about 2/3. Alternate treatments lacking CYP3A4 inducing activity should be considered. If an alternative treatment is unavailable, a Tarceva® dose greater than 150 mg should be considered for NSCLC patients, and greater than 100 mg considered for pancreatic cancer patients. If the Tarceva® dose is adjusted upward, the dose will need to be reduced upon discontinuation of rifampicin or other inducers. Other CYP3A4 inducers include, but are not limited to, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital and St. John's Wort.

Adverse Drug Reactions

When used as a monotherapy for NSCLC, the most common side effects were mild to moderate rash and diarrhea. Severe rash and diarrhea (9% & 6% NCI-CTC Grades 3-4, respectively) each resulted in 1% of Tarceva-treated patients discontinuing the single-agent Phase III trial.

When used in combination with gemcitabine for pancreatic cancer, the most common side effects were fatigue, rash, nausea, anorexia and diarrhea. Severe rash and diarrhea (5% and 5% NCI-CTC Grades 3-4, respectively) each resulted in dose reductions in 2% of patients, and discontinuation in up to 1% of patients receiving Tarceva plus gemcitabine. Myocardial infarction/ischemia occurred in 2.3% (1 fatal case) of patients in the Tarceva plus gemcitabine arm vs 1.2% (1 fatal case) in placebo plus gemcitabine arm. Also, 2.3% (1 fatal case) of patients in the Tarceva plus gemcitabine arm developed cerebrovascular accidents vs no cerebrovascular accidents in the placebo plus gemcitabine arm. Moreover, 0.8% of patients developed microangiopathic hemolytic anemia with thrombocytopenia in the Tarceva plus gemcitabine arm vs no cases in the placebo plus gemcitabine arm.

In both trials involving NSCLC and pancreatic cancer, NCI-CTC Grade 3 conjunctivitis and keratitis have been reported infrequently in patients receiving Tarceva therapy. Corneal ulcerations may also occur.

Pulmonary Toxicity

There have been infrequent reports of serious Interstitial Lung Disease (ILD)-like events, including fatalities, in patients receiving Tarceva. The overall incidence of ILD-like events in Tarceva-treated patients from all studies was approximately 0.7%. In NSCLC, single-agent Phase III study incidence was 0.8%, about the same as placebo. In pancreatic cancer, in combination with gemcitabine study incidence was 2.5% in the Tarceva plus gemcitabine arm vs 0.4% in the placebo plus gemcitabine arm.

Reported diagnoses in patients suspected of having ILD-like events included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, ILD, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome and lung infiltration. Symptoms started from 5 days to more than 9 months (median 39 days) after the initiation of Tarceva therapy.

Tarceva should be interrupted for acute onset of new or progressive unexplained pulmonary symptoms, and if ILD is diagnosed, Tarceva should be discontinued.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Erlotinib has not been tested for carcinogenicity.

Erlotinib has been tested for genotoxicity in a series of *in vitro* assays (bacterial mutation, human lymphocyte chromosome aberration, and mammalian cell mutation) and an in vivo mouse bone marrow micronucleus test and did not cause genetic damage. Erlotinib did not impair fertility in either male or female rats.

Table : Adverse Events Occurring in ≥10% of Single-Agent TARCEVA-treated Non-Small Cell Lung Cancer Patients (2:1 Randomization of TARCEVA to Placebo)

	TARCEVA 150 mg N = 485			**Placebo N = 242**		
NCI CTC Grade	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
MedDRA Preferred Term	**%**	**%**	**%**	**%**	**%**	**%**
Rash	75	8	<1	17	0	0
Diarrhea	54	6	<1	18	<1	0
Anorexia	52	8	1	38	5	<1
Fatigue	52	14	4	45	16	4
Dyspnea	41	17	11	35	15	11

Cough	33	4	0	29	2	0
Nausea	33	3	0	24	2	0
Infection	24	4	0	15	2	0
Vomiting	23	2	<1	19	2	0
Stomatitis	17	<1	0	3	0	0
Pruritus	13	<1	0	5	0	0
Dry skin	12	0	0	4	0	0
Conjunctivitis	12	<1	0	2	<1	0
Keratoconjunctivitis sicca	12	0	0	3	0	0
Abdominal pain	11	2	<1	7	1	<1

Comparison of adverse drug reactions between Tarceva and Irressa

According to the trial comparing erlotinib and gefitinib, EGFR-TKIs as a class are generally well tolerated. The two most common toxicities include dermatologic (acneiform rash and dry skin) and GI (diarrhea) side effects. [4,10] These effects are typically mild to moderate, easily managed, and reversible. [11]With gefitinib, the frequency of drug-related adverse events was dose dependent, with more frequent side effects occurring in patients receiving 500 mg/d compared with those receiving 250 mg/d. There is no evidence that the toxicity of gefitinib is cumulative with successive cycles of treatment.

In postmarketing use in Japan, interstitial lung disease (ILD) has emerged as a rare but serious complication of gefitinib use. [12] Worldwide, the rate of ILD associated with gefitinib in compassionate-use programs or postmarketing use is < 1%, and the mortality rate is approximately 0.3%. [13] In phase III trials [14,15] comparing standard chemotherapy doublets with or without gefitinib, the rates of ILD were lower and were not significantly different from placebo.

In the BR.21 study of erlotinib [28], ILD was also observed at an incidence of < 1%, which was not significantly different from placebo.

It should be noted that standard treatments for lung cancer such as chemotherapy and radiotherapy have an associated incidence of ILD of approximately 1%. ILD should be considered in any patient receiving treatment for lung cancer who has new-onset or worsening dyspnea or has unexplained new infiltrates on radiography, and chemotherapy drugs including the EGFR-TKIs should be discontinued while the appropriate clinical workup is conducted. Acute pneumonitis can resolve with

discontinuation of therapy with or without a short course of corticosteroids. However, once fibrosis has occurred, there may be irreversible loss of lung function, and a mortality rate of up to 50% in this patient subgroup can be expected. [17]

Comparison with Iressa (Gefitinib)

Iressa (Gefitinib)		Tarceva (Erlotinib)	
Trial	Results	Trial	Results
Phase I [1,2,3]	Diarrhea or rash occurred in 50% to 60% of patients. Diarrhea was the dose-limiting toxicity in each trial.	Phase I [6]	The most common side effects were rash and diarrhea, and diarrhea was the dose-limiting toxicity at a continuous daily dose of 200 mg.
Phase II IDEAL –1 [4]	Toxicities for both doses (500-mg dose versus the 250-mg dose) were relatively mild, with approximately 40% to 50% of patients experiencing grade I/II diarrhea or rash. There was, however, a slightly higher incidence of grade 3 toxicity for the 500-mg dose versus the 250-mg dose (4.7% versus 1.5%, respectively).	Phase II [7,8,9]	Mild rash and diarrhea occurred in 75% and 61% of the patients, respectively. Grade 3 rash (2%) and diarrhea (2%), however, were uncommon.
Phase II IDEAL-2 [5]	The most common side effects were mild rash and diarrhea, and similar to the other phase II trial, there was a slightly increased incidence of grade 3 toxicities with the higher dose.		

Precautions

Pregnancy and Lactation

Tarceva is pregnancy category D.

There are no adequate and well-controlled studies in pregnant women using Tarceva. When receiving Tarceva, women of childbearing potential should be advised to avoid pregnancy and pregnant women apprised of the potential risks to the fetus. Tarceva should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the fetus.

It is not known whether erlotinib is excreted in human milk. Because many drugs are excreted in human milk and because the effects of TARCEVA on infants have not been studied Women receiving Tarceva should be advised against breastfeeding.

Paeditric Use

The safety and effectiveness of TARCEVA in pediatric patients have not been studied.

Geriatric Use

No meaningful differences in safety or pharmacokinetics were observed between younger and older patients in clinical trials. Therefore, no dosage adjustments are recommended in elderly patients.

Hepatotoxicity

Liver function test abnormalities have been observed following the administration of Tarceva. Periodic liver function testing should be considered, and Tarceva dose modification should be considered if changes in liver function are severe.
Erlotinib is eliminated by hepatic metabolism and biliary excretion. Therefore, caution should be used when administering Tarceva to patients with hepatic impairment. Dose reduction or interruption of Tarceva should be considered if severe adverse reactions occur.

Contraindications

No contraindications.

Cost Comparison

Drug/cost	Daily cost	Monthly cost
Tarceva	$90.00	$2700.00
Irressa	$72.50	$2175.30

Reference

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