HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TARCEVA safely and effectively. See full prescribing information for TARCEVA.

TARCEVA® (erlotinib) tablets, oral

Initial U.S. Approval: 2004

----------RECENT MAJOR CHANGES----------

Warnings and Precautions, Elevated International Normalized Ratio and Potential Bleeding 04/2012

----------INDICATIONS AND USAGE----------

TARCEVA is a kinase inhibitor indicated for:

- Maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. (1.1)
- Treatment of locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. (1.1)
- First-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine. (1.2)

----------DOSAGE AND ADMINISTRATION----------

- The dose for NSCLC is 150 mg/day. (2.1)
- The dose for pancreatic cancer is 100 mg/day. (2.2)
- All doses of TARCEVA should be taken on an empty stomach at least one hour before or two hours after food. (2.1, 2.2)
- Reduce in 50 mg decrements, when necessary. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 25 mg, 100 mg and 150 mg. (3)

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Interstitial Lung Disease (ILD)-like events, including fatalities have been infrequently reported. Interrupt TARCEVA if acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever occur. Discontinue TARCEVA if ILD is diagnosed. (5.1)
- Cases of acute renal failure (including fatalities), and renal insufficiency have been reported. Interrupt TARCEVA in the event of dehydration. Monitor renal function and electrolytes in patients at risk of dehydration. (5.2)
- Cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported. Monitor periodic liver function testing. Interrupt or discontinue TARCEVA if liver function changes are severe. (5.3)
- Monitor patients with hepatic impairment closely. Interrupt or discontinue TARCEVA if changes in liver function are severe (5.4)
- Gastrointestinal perforations, including fatalities, have been reported. Discontinue TARCEVA. (5.5)
- Bullous and exfoliative skin disorders, including fatalities, have been reported. Interrupt or discontinue TARCEVA (5.6)
- Myocardial infarction/ischemia has been reported, including fatalities, in patients with pancreatic cancer. (5.7)
- Cerebrovascular accidents, including a fatality, have been reported in patients with pancreatic cancer. (5.8)
- Microangiopathic Hemolytic Anemia with thrombocytopenia has been reported in patients with pancreatic cancer. (5.9)
- Corneal perforation and ulceration have been reported. Interrupt or discontinue TARCEVA (5.10)
- International Normalized Ratio (INR) elevations and bleeding events (including fatalities), associated with concomitant warfarin administration have been reported. Monitor patients taking warfarin or other coumarin-derivative anticoagulants. (5.11)
- TARCEVA can cause fetal harm when administered to a pregnant woman. Women should be advised to avoid pregnancy while on TARCEVA. (5.12)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (>20%) in maintenance treatment are rash-like events and diarrhea. (6)
- The most common adverse reactions (>20%) in 2nd line NSCLC are rash, diarrhea, anorexia, fatigue, dyspnea, cough, nausea, infection and vomiting. (6)
- The most common adverse reactions (>20%) in pancreatic cancer are fatigue, rash, nausea, anorexia, diarrhea, abdominal pain, vomiting, weight decrease, infection, edema, pyrexia, constipation, bone pain, dyspnea, stomatitis and myalgia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact OSI Pharmaceuticals, LLC, at 1-800-572-1932 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- CYP3A4 inhibitors may increase erlotinib plasma concentrations. (7)
- CYP3A4 inducers may decrease erlotinib plasma concentrations. (7)
- CYP1A2 inducers may decrease erlotinib plasma concentrations. (7)
- Erlotinib solubility is pH dependent. Drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and hence its absorption. (7)
- Cigarette smoking decreases erlotinib plasma concentrations (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: [04/2012]

FULL PRESCRIBING INFORMATION: CONTENTS *

1 INDICATIONS AND USAGE
- 1.1 Non-Small Cell Lung Cancer (NSCLC)
- 1.2 Pancreatic Cancer

2 DOSAGE AND ADMINISTRATION
- 2.1 Recommended Dose - NSCLC
- 2.2 Recommended Dose – Pancreatic Cancer
- 2.3 Dose Modifications

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Pulmonary Toxicity
- 5.2 Renal Failure
- 5.3 Hepatotoxicity
- 5.4 Patients with Hepatic Impairment
- 5.5 Gastrointestinal perforation
- 5.6 Bullous and exfoliative skin disorders
- 5.7 Myocardial infarction/ischemia
- 5.8 Cerebrovascular accident
- 5.9 Microangiopathic Hemolytic Anemia with Thrombocytopenia
- 5.10 Ocular Disorders
- 5.11 Elevated International Normalized Ratio and Potential Bleeding
- 5.12 Use in Pregnancy

6 ADVERSE REACTIONS
- 6.1 Clinical Trial Experience
- 6.2 Post-Marketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Gender
- 8.7 Race
- 8.8 Patients with Hepatic Impairment
- 8.9 Patients with Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
- 14.1 Non-Small Cell Lung Cancer (NSCLC) – TARCEVA monotherapy administered as maintenance treatment
- 14.2 NSCLC - TARCEVA administered as a Single-agent
- 14.3 NSCLC - TARCEVA Administered Concurrently with Chemotherapy
- 14.4 Pancreatic Cancer – TARCEVA Administered Concurrently with Gemcitabine

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Non-Small Cell Lung Cancer (NSCLC)

TARCEVA monotherapy is indicated for the maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer whose disease has not progressed after four cycles of platinum-based first-line chemotherapy *[see Clinical Studies (14.1)]*.

TARCEVA 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 *[see Clinical Studies (14.2)]*.

Results from two, multicenter, placebo-controlled, randomized, Phase 3 trials conducted in first-line patients with locally advanced or metastatic NSCLC showed no clinical benefit with the concurrent administration of TARCEVA with platinum-based chemotherapy [carboplatin and paclitaxel or gemcitabine and cisplatin] and its use is not recommended in that setting *[see Clinical Studies (14.3)]*.

1.2 Pancreatic Cancer

TARCEVA in combination with gemcitabine is indicated for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer *[see Clinical Studies (14.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 NSCLC

The recommended daily dose of TARCEVA for NSCLC is 150 mg taken on an empty stomach at least one hour before or two hours after the ingestion of food. Treatment should continue until disease progression or unacceptable toxicity occurs. There is no evidence that treatment beyond progression is beneficial.

2.2 Pancreatic Cancer

The recommended daily dose of TARCEVA for pancreatic cancer is 100 mg taken on an empty stomach at least one hour before or two hours after the ingestion of food, in combination with gemcitabine *[see Clinical Studies (14.4) or the gemcitabine package insert]*. Treatment should continue until disease progression or unacceptable toxicity occurs.

2.3 Dose Modifications

In patients who develop an acute onset of new or progressive pulmonary symptoms, such as dyspnea, cough or fever, treatment with TARCEVA should be interrupted pending diagnostic evaluation. If Interstitial Lung Disease (ILD) is diagnosed, TARCEVA should be discontinued and appropriate treatment instituted as necessary *[see Warnings and Precautions (5.1)]*. Discontinue TARCEVA for hepatic failure or gastrointestinal perforation. Interrupt or discontinue TARCEVA in patients with dehydration who are at risk for renal failure, in patients with severe bullous, blistering or exfoliative skin conditions, or in patients with acute /worsening ocular disorders *[see Warnings and Precautions (5.2, 5.3, 5.4, 5.5, 5.6, 5.10)]*.

Diarrhea can usually be managed with loperamide. Patients with severe diarrhea who are unresponsive to loperamide or who become dehydrated may require dose reduction or temporary interruption of therapy. Patients with severe skin reactions may also require dose reduction or temporary interruption of therapy.

When dose reduction is necessary, the TARCEVA dose should be reduced in 50 mg decrements.

In patients who are taking TARCEVA with a strong CYP3A4 inhibitor such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), voriconazole, or grapefruit or grapefruit juice, a dose reduction should be considered if severe adverse reactions occur. Similarly, in patients who are taking TARCEVA with an inhibitor of both CYP3A4 and CYP1A2 like ciprofloxacin, a dose reduction of TARCEVA should be considered if severe adverse reactions occur *[see Drug Interactions (7)]*.

Pre-treatment with the CYP3A4 inducer rifampicin decreased erlotinib AUC by about 2/3 to 4/5. Use of alternative treatments lacking CYP3A4 inducing activity is strongly recommended. If an alternative treatment is unavailable, an increase in the dose of TARCEVA should be considered as tolerated at two week intervals while monitoring the patient's safety. The maximum dose of TARCEVA studied in combination with rifampicin is 450 mg. If the TARCEVA dose is adjusted upward, the dose will need to be reduced immediately to the indicated starting dose 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. These too should be avoided if possible *[see Drug Interactions (7)]*.

Cigarette smoking has been shown to reduce erlotinib exposure. Patients should be advised to stop smoking. If a patient continues to smoke, a cautious increase in the dose of TARCEVA, not exceeding 300 mg may be considered, while monitoring the patient's safety. However, efficacy and long-term safety (> 14 days) of a dose higher than the recommended starting doses have not been established in patients who continue to smoke cigarettes. If the TARCEVA dose is adjusted upward, the dose should be reduced immediately to the indicated starting dose upon cessation of smoking *[see Clinical Pharmacology (12.3)]*.

Erlotinib is eliminated by hepatic metabolism and biliary excretion. Although erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh B), patients with hepatic impairment (total bilirubin > ULN or Child-Pugh A, B and C) should be closely monitored during therapy with TARCEVA [*see Warnings and Precautions (5.4)]*. Treatment with TARCEVA should be used with extra caution in patients with total bilirubin > 3 x ULN. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside normal range. In the setting of worsening liver function tests, before they become severe, dose interruption and/or dose reduction with frequent liver function test monitoring should be considered. TARCEVA dosing should be interrupted or discontinued if total bilirubin is >3 x ULN and/or transaminases are >5 x ULN in the setting of normal pretreatment values *[see Warnings and Precautions (5.3, 5.4), Adverse Reactions (6.1, 6.2) and Use in Specific Populations (8.8]*.

3 DOSAGE FORMS AND STRENGTHS

25 mg tablets
White film-coated tablets for daily oral administration. Round, biconvex face and straight sides, white film-coated, printed in orange with a "T" and "25" on one side and plain on the other side.

100 mg tablets
White film-coated tablets for daily oral administration. Round, biconvex face and straight sides, white film-coated, printed in gray with "T" and "100" on one side and plain on the other side.

150 mg tablets
White film-coated tablets for daily oral administration. Round, biconvex face and straight sides, white film-coated, printed in maroon with "T" and "150" on one side and plain on the other side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pulmonary Toxicity

There have been reports of serious Interstitial Lung Disease (ILD)-like events, including fatalities, in patients receiving TARCEVA for treatment of NSCLC, pancreatic cancer or other advanced solid tumors. In the randomized single-agent NSCLC-studies *[see Clinical Studies (14.1, 14.2)]*, the incidence of serious ILD-like events in the TARCEVA treated patients versus placebo treated patients was 0.7% versus 0% in the maintenance study and 0.8% for both groups in the 2nd and 3rd line study. In the pancreatic cancer study - in combination with gemcitabine – *[see Clinical Studies (14.4)]*, the incidence of ILD-like events was 2.5% in the TARCEVA plus gemcitabine group vs. 0.4% in the placebo plus gemcitabine group.

The overall incidence of ILD-like events in approximately 32,000 TARCEVA-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) was approximately 1.1%.

Reported diagnoses in patients suspected of having ILD-like events included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, 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 initiating TARCEVA therapy. In the lung cancer trials most of the cases were associated with

confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections.

In the event of an acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, and fever, TARCEVA therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, TARCEVA should be discontinued and appropriate treatment instituted as needed *[see Dosage and Administration (2.3)]*.

5.2 Renal Failure

Cases of hepatorenal syndrome, acute renal failure (including fatalities), and renal insufficiency have been reported. Some were secondary to baseline hepatic impairment while others were associated with severe dehydration due to diarrhea, vomiting, and/or anorexia or concurrent chemotherapy use. In the event of dehydration, particularly in patients with contributing risk factors for renal failure (eg, pre-existing renal disease, medical conditions or medications that may lead to renal disease, or other predisposing conditions including advanced age), TARCEVA therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patient. Periodic monitoring of renal function and serum electrolytes is recommended in patients at risk of dehydration *[see Adverse Reactions (6.1) and Dosage and Administration (2.3)]*.

5.3 Hepatotoxicity

Cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported during use of TARCEVA, particularly in patients with baseline hepatic impairment. Therefore, periodic liver function testing (transaminases, bilirubin, and alkaline phosphatase) is recommended. In the setting of worsening liver function tests, dose interruption and/or dose reduction with frequent liver function test monitoring should be considered. TARCEVA dosing should be interrupted or discontinued if total bilirubin is >3 x ULN and/or transaminases are >5 x ULN in the setting of normal pretreatment values *[see Adverse Reactions (6.1, 6.2) and Dosage and Administration (2.3)]*.

5.4 Patients with Hepatic Impairment

In a pharmacokinetic study in patients with moderate hepatic impairment (Child-Pugh B) associated with significant liver tumor burden, 10 out of 15 patients died on treatment or within 30 days of the last TARCEVA dose. One patient died from hepatorenal syndrome, 1 patient died from rapidly progressing liver failure and the remaining 8 patients died from progressive disease. Six out of the 10 patients who died had baseline total bilirubin > 3 x ULN suggesting severe hepatic impairment. Treatment with TARCEVA should be used with extra caution in patients with total bilirubin > 3 x ULN. Patients with hepatic impairment (total bilirubin > ULN or Child-Pugh A, B and C) should be closely monitored during therapy with TARCEVA. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside normal range *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.3)]*.

5.5 Gastrointestinal Perforation

Gastrointestinal perforation (including fatalities) have been reported in patients receiving TARCEVA. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane-based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. *[see Adverse Reactions (6.1, 6.2)]*. Permanently discontinue TARCEVA in patients who develop gastrointestinal perforation.

5.6 Bullous and Exfoliative Skin Disorders

Bullous, blistering and exfoliative skin conditions have been reported including cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal *[see Adverse Reactions (6.1, 6.2)]*. Interrupt or discontinue TARCEVA treatment if the patient develops severe bullous, blistering or exfoliating conditions.

5.7 Myocardial Infarction/Ischemia

In the pancreatic carcinoma trial, six patients (incidence of 2.3%) in the TARCEVA/gemcitabine group developed myocardial infarction/ischemia. One of these patients died due to myocardial infarction. In comparison, 3 patients in the placebo/gemcitabine group developed myocardial infarction (incidence 1.2%) and one died due to myocardial infarction.

5.8 Cerebrovascular Accident

In the pancreatic carcinoma trial, six patients in the TARCEVA/gemcitabine group developed cerebrovascular accidents (incidence: 2.3%). One of these was hemorrhagic and was the only fatal event. In comparison, in the placebo/gemcitabine group there were no cerebrovascular accidents.

5.9 Microangiopathic Hemolytic Anemia with Thrombocytopenia

In the pancreatic carcinoma trial, two patients in the TARCEVA/gemcitabine group developed microangiopathic hemolytic anemia with thrombocytopenia (incidence: 0.8%). Both patients received TARCEVA and gemcitabine concurrently. In comparison, in the placebo/gemcitabine group there were no cases of microangiopathic hemolytic anemia with thrombocytopenia.

5.10 Ocular Disorders

Corneal perforation or ulceration have been reported during use of TARCEVA. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with TARCEVA treatment and are known risk factors for corneal ulceration/perforation *[see Adverse Reactions (6.1)]*. Interrupt or discontinue TARCEVA therapy if patients present with acute/worsening ocular disorders such as eye pain.

5.11 Elevated International Normalized Ratio and Potential Bleeding

International Normalized Ratio (INR) elevations and bleeding events, including gastrointestinal and non-gastrointestinal bleeding (including fatalities), have been reported, associated with concomitant warfarin administration. Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR *[see Adverse Reactions (6.1) and Drug Interactions (7)]*.

5.12 Use in Pregnancy

TARCEVA can cause fetal harm when administered to a pregnant woman. Erlotinib administered to rabbits during organogenesis at doses that result in plasma drug concentrations of approximately 3 times those in humans at the recommended dose of 150 mg daily, was associated with embryofetal lethality and abortion. When erlotinib was administered to female rats prior to mating and through the first week of pregnancy, at doses 0.3 or 0.7 times the clinical dose of 150 mg, on a mg/m^2 basis, there was an increase in early resorptions that resulted in a decrease in the number of live fetuses *[see Use in Specific Populations (8.1)]*.

There are no adequate and well-controlled studies in pregnant women using TARCEVA. Women of childbearing potential should 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. If TARCEVA is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety evaluation of TARCEVA is based on more than 1200 cancer patients who received TARCEVA as monotherapy, more than 300 patients who received TARCEVA 100 or 150 mg plus gemcitabine, and 1228 patients who received TARCEVA concurrently with other chemotherapies.

There have been reports of serious events, including fatalities, in patients receiving TARCEVA for treatment of NSCLC, pancreatic cancer or other advanced solid tumors *[see Warnings and Precautions (5) and Dosage and Administration (2.3)]*.

6.1 Clinical Trial Experience

Non-Small Cell Lung Cancer

Maintenance Study

Adverse reactions, regardless of causality, that occurred in at least 3% of patients treated with single-agent TARCEVA at 150 mg and at least 3% more often than in the placebo group in the randomized maintenance trial are summarized by NCI-CTC (version 3.0) Grade in Table 1.

The most common adverse reactions in patients receiving single-agent TARCEVA 150 mg were rash and diarrhea. Grade 3/4 rash and diarrhea occurred in 6.0% and 1.8%, respectively, in TARCEVA-treated patients. Rash and diarrhea resulted in study discontinuation in 1.2% and 0.5% of TARCEVA-treated patients, respectively. Dose reduction or interruption for rash and diarrhea was needed in 5.1% and 2.8% of patients, respectively. In TARCEVA-treated patients who developed rash, the onset was within two weeks in 66% and within one month in 81%.

Table 1: NSCLC Maintenance Study: Adverse Reactions Occurring More Frequently (≥ 3%) in the Single-Agent TARCEVA Group than in the Placebo Group and in ≥ 3% of Patients in the TARCEVA Group.

	TARCEVA N = 433			**PLACEBO N = 445**		
NCI-CTC Grade	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
MedDRA Preferred Term	%	%	%	%	%	%
Rash	49.2	6.0	0	5.8	0	0
Diarrhea	20.3	1.8	0	4.5	0	0
Fatigue	9.0	1.8	0	5.8	1.1	0
Anorexia	9.2	<1	0	4.9	<1	0
Pruritus	7.4	<1	0	2.7	0	0
Acne	6.2	<1	0	0	0	0
Dermatitis Acneiform	4.6	<1	0	1.1	0	0
Dry Skin	4.4	0	0	<1	0	0
Weight Decreased	3.9	<1	0	<1	0	0
Paronychia	3.9	<1	0	0	0	0

Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) were observed in patients receiving single-agent TARCEVA 150 mg in the Maintenance study. Grade 2 (>2.5 – 5.0 x ULN) ALT elevations occurred in 2% and 1%, and Grade 3 (>5.0 – 20.0 x ULN) ALT elevations were observed in 1% and 0% of TARCEVA and placebo treated patients, respectively. The TARCEVA treatment group had Grade 2 (>1.5-3.0 x ULN) bilirubin elevations in 4% and Grade 3 (>3.0-10.0 x ULN) in <1% compared with <1% for both Grades 2 and 3 in the placebo group. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe *[see Dosage and Administration (2.3)]*.

Second/Third Line Study

Adverse reactions, regardless of causality, that occurred in at least 10% of patients treated with single-agent TARCEVA at 150 mg and at least 3% more often than in the placebo group in the randomized trial of patients with NSCLC are summarized by NCI-CTC (version 2.0) Grade in Table 2.

The most common adverse reactions in this patient population were rash and diarrhea. Grade 3/4 rash and diarrhea occurred in 9% and 6%, respectively, in TARCEVA-treated patients. Rash and diarrhea each resulted in study discontinuation in 1% of TARCEVA-treated patients. Six percent and 1% of patients needed dose reduction for rash and diarrhea, respectively. The median time to onset of rash was 8 days, and the median time to onset of diarrhea was 12 days.

Table 2: NSCLC 2nd/3rd Line Study: Adverse Reactions Occurring More Frequently (≥ 3%) in the Single-agent TARCEVA 150 mg Group than in the Placebo Group and in ≥10% of Patients in the TARCEVA Group.

	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

Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) were observed in patients receiving single-agent TARCEVA 150 mg. These elevations were mainly transient or associated with liver metastases. Grade 2 (>2.5 – 5.0 x ULN) ALT elevations occurred in 4% and <1% of TARCEVA and placebo treated patients, respectively. Grade 3 (>5.0 – 20.0 x ULN) elevations were not observed in TARCEVA-treated patients. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe *[see Dosage and Administration (2.3)]*.

Pancreatic Cancer

Adverse reactions, regardless of causality, that occurred in at least 10% of patients treated with TARCEVA 100 mg plus gemcitabine in the randomized trial of patients with pancreatic cancer are summarized by NCI-CTC (version 2.0) Grade in Table 3.

The most common adverse reactions in pancreatic cancer patients receiving TARCEVA 100 mg plus gemcitabine were fatigue, rash, nausea, anorexia and diarrhea. In the TARCEVA plus gemcitabine arm, Grade 3/4 rash and diarrhea were each reported in 5% of TARCEVA plus gemcitabine-treated patients. The median time to onset of rash and diarrhea was 10 days and 15 days, respectively. Rash and diarrhea each resulted in dose reductions in 2% of patients, and resulted in study discontinuation in up to 1% of patients receiving TARCEVA plus gemcitabine. The 150 mg cohort was associated with a higher rate of certain class-specific adverse reactions including rash and required more frequent dose reduction or interruption.

Table 3: Adverse Reactions Occurring in ≥ 10% of TARCEVA-treated Pancreatic Cancer Patients: 100 mg cohort

	TARCEVA + Gemcitabine 1000 mg/m^2 IV N=259			**Placebo + Gemcitabine 1000 mg/m^2 IV N=256**		
NCI-CTC Grade	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
MedDRA Preferred Term	**%**	**%**	**%**	**%**	**%**	**%**
Fatigue	73	14	2	70	13	2
Rash	69	5	0	30	1	0
Nausea	60	7	0	58	7	0
Anorexia	52	6	<1	52	5	<1
Diarrhea	48	5	<1	36	2	0
Abdominal pain	46	9	<1	45	12	<1
Vomiting	42	7	<1	41	4	<1
Weight decreased	39	2	0	29	<1	0
Infection*	39	13	3	30	9	2
Edema	37	3	<1	36	2	<1
Pyrexia	36	3	0	30	4	0
Constipation	31	3	1	34	5	1
Bone pain	25	4	<1	23	2	0
Dyspnea	24	5	<1	23	5	0
Stomatitis	22	<1	0	12	0	0
Myalgia	21	1	0	20	<1	0

	TARCEVA + Gemcitabine 1000 mg/m^2 IV N=259			Placebo + Gemcitabine 1000 mg/m^2 IV N=256		
NCI-CTC Grade	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Depression	19	2	0	14	<1	0
Dyspepsia	17	<1	0	13	<1	0
Cough	16	0	0	11	0	0
Dizziness	15	<1	0	13	0	<1
Headache	15	<1	0	10	0	0
Insomnia	15	<1	0	16	<1	0
Alopecia	14	0	0	11	0	0
Anxiety	13	1	0	11	<1	0
Neuropathy	13	1	<1	10	<1	0
Flatulence	13	0	0	9	<1	0
Rigors	12	0	0	9	0	0

*Includes all MedDRA preferred terms in the Infections and Infestations System Organ Class

In the pancreatic carcinoma trial, 10 patients in the TARCEVA/gemcitabine group developed deep venous thrombosis (incidence: 3.9%). In comparison, 3 patients in the placebo/gemcitabine group developed deep venous thrombosis (incidence 1.2%). The overall incidence of grade 3 or 4 thrombotic events, including deep venous thrombosis, was similar in the two treatment arms: 11% for TARCEVA plus gemcitabine and 9% for placebo plus gemcitabine.

No differences in Grade 3 or Grade 4 hematologic laboratory toxicities were detected between the TARCEVA plus gemcitabine group compared to the placebo plus gemcitabine group.

Severe adverse reactions (≥grade 3 NCI-CTC) in the TARCEVA plus gemcitabine group with incidences < 5% included syncope, arrhythmias, ileus, pancreatitis, hemolytic anemia including microangiopathic hemolytic anemia with thrombocytopenia, myocardial infarction/ischemia, cerebrovascular accidents including cerebral hemorrhage, and renal insufficiency *[see Warnings and Precautions (5)]*.

Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) have been observed following the administration of TARCEVA plus gemcitabine in patients with pancreatic cancer. Table 4 displays the most severe NCI-CTC grade of liver function abnormalities that developed. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe *[see Dosage and Administration (2.3)]*.

Table 4 Liver Function Test Abnormalities (most severe NCI-CTC grade) in Pancreatic Cancer Patients: 100 mg Cohort

	TARCEVA + Gemcitabine 1000 mg/m^2 IV N = 259			Placebo + Gemcitabine 1000 mg/m^2 IV N = 256		
NCI-CTC Grade	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**
Bilirubin	17 %	10%	<1%	11%	10%	3%
ALT	31%	13%	<1%	22%	9%	0%

Of the total number of patients participating in the randomized NSCLC Maintenance trial, 66% were less than 65 years of age, and 34% of patients were aged 65 years or older. The hazard ratio for overall survival was 0.78 (95% CI: 0.65, 0.95) in patients less than 65 years of age and 0.88 (95% CI: 0.68, 1.15) in patients who were 65 years or older.

Second/Third Line Study

Of the total number of patients participating in the randomized 2nd/3rd line NSCLC trial, 61% were less than 65 years of age, and 39% of patients were aged 65 years or older. The survival benefit was maintained across both age groups [OS HR = 0.75 (95% CI: 0.6, 0.9) in patients less than 65 years of age, and OS HR = 0.79 (95% CI: 0.6, 1.0) in patients who were 65 years or older].

First-Line Pancreatic Cancer

In the pancreatic cancer study, 52 % of patients were younger than 65 years of age and 48 % were 65 years of age or older. There were no clinically relevant survival differences between the age groups [OS HR = 0.78 (95% CI: 0.6, 1.0) in patients less than 65 years of age, and OS HR = 0.94 (95% CI: 0.7, 1.2) in patients who were 65 years or older]. No meaningful differences in safety or pharmacokinetics were observed between younger and older patients in these studies. Therefore, no dosage adjustments are recommended in elderly patients.

8.6 Gender

Maintenance Study

Of the total number of patients participating in the randomized Maintenance trial, 73% were males and 27% females. There were no clinically relevant differences in safety and efficacy based on gender [OS HR = 0.88 (95% CI: 0.74, 1.05) in males and OS HR = 0.64 (95% CI: 0.46, 0.91) in females].

Second/Third Line Study

Of the total number of patients participating in the randomized 2nd/3rd line NSCLC trial, 65% were males and 35% females. There were no clinically relevant differences in safety and efficacy based on gender [OS HR = 0.76 (95% CI: 0.6, 0.9) in males and OS HR = 0.80 (95% CI: 0.6, 1.1) in females].

First Line Pancreatic Cancer

In the pancreatic cancer study, 51% of patients were males and 49% females. There were no clinically relevant differences in safety and efficacy based on gender [OS HR = 0.74 (95% CI: 0.6, 0.9) in males and OS HR = 1.0 (95% CI: 0.8, 1.3) in females].

8.7 Race

Maintenance Study

In the randomized Maintenance trial, 84% of all patients were Caucasian and 15% were Asian. There were no clinically relevant differences in safety and efficacy based on race [OS HR = 0.86 (95% CI: 0.73, 1.01) in Caucasians and OS HR = 0.66 (95% CI: 0.42, 1.05) in Asians].

Second/Third Line Study

In the randomized 2nd/3rd line NSCLC trial, 78% of all patients were Caucasian and 13% were Asian. There were no clinically relevant differences in safety and efficacy based on race [OS HR = 0.79 (95% CI: 0.6, 1.0) in Caucasians and OS HR = 0.61 (95% CI: 0.4, 1.0) in Asians].

First-Line Pancreatic Cancer

In the pancreatic cancer study, 86% of all patients were Caucasian and 8% were Asian. There were no clinically relevant differences in safety and efficacy based on race [OS HR = 0.88 (95% CI: 0.7, 1.1) in Caucasians and OS HR = 0.61 (95% CI: 0.3, 1.3) in Asians].

	TARCEVA (N = 488)		Placebo (N = 243)	
Best Response to Prior Therapy at Baseline*				
CR/PR	196	(40)	96	(40)
PD	101	(21)	51	(21)
SD	191	(39)	96	(40)
Number of Prior Regimens at Baseline*				
1	243	(50)	121	(50)
2	238	(49)	119	(49)
3	7	(1)	3	(1)
Exposure to Prior Platinum at Baseline*				
Yes	454	(93)	224	(92)
No	34	(7)	19	(8)

* Stratification factor as documented at baseline; distribution differs slightly from values reported at time of randomization.

The results of the study are shown in Table 8.

Table 8: Efficacy Results

	TARCEVA	Placebo	Hazard Ratio (1)	95% CI	p-value
Survival	Median 6.7 mo	Median 4.7 mo	0.73	0.61 – 0.86	<0.001 (2)
1-year Survival	31.2%	21.5%			
Progression-Free Survival	Median 9.9 wk	Median 7.9 wk	0.59	0.50 – 0.70	<0.001 (2)
Tumor Response (CR+PR)	8.9%	0.9%			<0.001 (3)
Response Duration	Median 34.3 wk	Median 15.9 wk			

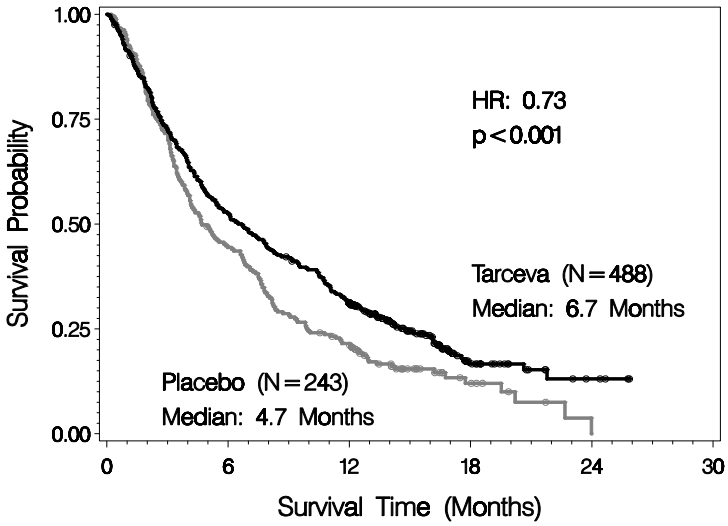
(1) Cox regression model with the following covariates: ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy.

(2) Two-sided Log-Rank test stratified by ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy.

(3) Two-sided Fisher's exact test

Survival was evaluated in the intent-to-treat population. Figure 2 depicts the Kaplan-Meier curves for overall survival. The primary survival and PFS analyses were two-sided Log-Rank tests stratified by ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy.

Figure 2: Kaplan – Meier Curve for Overall Survival of Patients by Treatment Group



Note: HR is from Cox regression model with the following covariates: ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy. P-value is from two-sided Log-Rank test stratified by ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy.

14.3 NSCLC - TARCEVA Administered Concurrently with Chemotherapy

Results from two, multicenter, placebo-controlled, randomized, trials in over 1000 patients conducted in first-line patients with locally advanced or metastatic NSCLC showed no clinical benefit with the concurrent administration of TARCEVA with platinum-based chemotherapy [carboplatin and paclitaxel (TARCEVA, N = 526) or gemcitabine and cisplatin (TARCEVA, N = 580)].

14.4 Pancreatic Cancer - TARCEVA Administered Concurrently with Gemcitabine

The efficacy and safety of TARCEVA in combination with gemcitabine as a first-line treatment was assessed in a randomized, double blind, placebo-controlled trial in 569 patients with locally advanced, unresectable or metastatic pancreatic cancer. Patients were randomized 1:1 to receive TARCEVA (100 mg or 150 mg) or placebo once daily on a continuous schedule plus gemcitabine IV (1000 mg/m^2, Cycle 1 - Days 1, 8, 15, 22, 29, 36 and 43 of an 8 week cycle; Cycle 2 and subsequent cycles - Days 1, 8 and 15 of a 4 week cycle [the approved dose and schedule for pancreatic cancer, see the gemcitabine package insert]). TARCEVA or placebo was taken orally once daily until disease progression or unacceptable toxicity. The primary endpoint was survival. Secondary endpoints included response rate, and progression-free survival (PFS). Duration of response was also examined. The study was conducted in 18 countries. A total of 285 patients were randomized to receive gemcitabine plus TARCEVA (261 patients in the 100 mg cohort and 24 patients in the 150 mg cohort) and 284 patients were randomized to receive gemcitabine plus placebo (260 patients in the 100 mg cohort and 24 patients in the 150 mg cohort). Too few patients were treated in the 150 mg cohort to draw conclusions.

Table 9 summarizes the demographic and disease characteristics of the study population that was randomized to receive 100 mg of TARCEVA plus gemcitabine or placebo plus gemcitabine. Baseline demographic and disease characteristics of the patients were similar between the 2 treatment groups, except for a slightly larger proportion of females in the TARCEVA arm (51%) compared with the placebo arm (44%). The median time from initial diagnosis to randomization was approximately 1.0 month. Most patients presented with metastatic disease at study entry as the initial manifestation of pancreatic cancer.

Table 9: Demographic and Disease Characteristics: 100 mg Cohort

	TARCEVA+ Gemcitabine (N=261)		Placebo + Gemcitabine (N=260)	
Characteristics	**N**	**(%)**	**N**	**(%)**
Gender				
Female	134	(51)	114	(44)
Male	127	(49)	146	(56)
Age (Years)				
<65	136	(52)	138	(53)
≥65	125	(48)	122	(47)
Race				
Caucasian	225	(86)	231	(89)
Black	8	(3)	5	(2)
Asian	20	(8)	14	(5)
Other	8	(3)	10	(3)
ECOG Performance Status*				
0	82	(31)	83	(32)
1	134	(51)	132	(51)
2	44	(17)	45	(17)
Unknown*	1	(<1)	0	(0)
Disease Status at Baseline**				
Locally Advanced	61	(23)	63	(24)
Distant Metastasis	200	(77)	197	(76)

*Unknown includes responses of 'Unknown' and missing.

**Stratification factor as documented at baseline; distribution differs slightly from values reported at time of randomization.

The results of the study are shown in Table 10.

Table 10: Efficacy Results: 100 mg Cohort

	TARCEVA + Gemcitabine	Placebo+ Gemcitabine	Hazard Ratio (1)	95% CI	p-value
Survival	Median 6.4 mo 250 deaths	Median 6.0 mo 254 deaths	0.81	0.68 – 0.97	0.028 (2)
1-year Survival	23.8%	19.4%			
Progression-Free Survival	Median 3.8 mo 225 events	Median 3.5 mo 232 events	0.76	0.64 – 0.92	0.006 (2)
Tumor Response (CR+PR)	8.6%	7.9%			0.87 (3)
Response Duration	Median 23.9 wk	Median 23.3 wk			

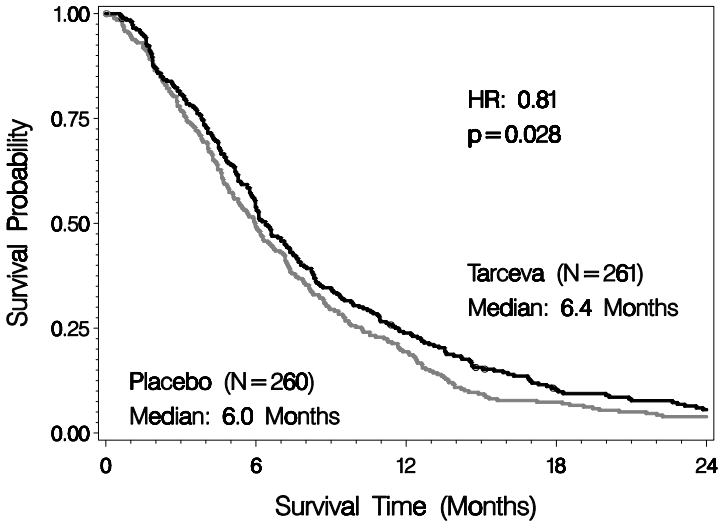
(1) Cox regression model with the following covariates: ECOG performance status, and extent of disease.

(2) Two-sided Log-Rank test stratified by ECOG performance status and extent of disease.

(3) Two-sided Fisher's exact test.

Survival was evaluated in the intent-to-treat population. Figure 3 depicts the Kaplan-Meier curves for overall survival in the 100 mg cohort. The primary survival and PFS analyses were two-sided Log-Rank tests stratified by ECOG performance status and extent of disease.

Figure 3: Kaplan – Meier Curve for Overall Survival: 100 mg Cohort



Note: HR is from Cox regression model with the following covariates: ECOG performance status and extent of disease. P-value is from two-sided Log-Rank test stratified by ECOG performance status and extent of disease.

16 HOW SUPPLIED/STORAGE AND HANDLING

25 mg Tablets

Round, biconvex face and straight sides, white film-coated, printed in orange with a "T" and "25" on one side and plain on the other side; supplied in:

Bottles of 30: NDC 50242-062-01

100 mg Tablets

Round, biconvex face and straight sides, white film-coated, printed in gray with “T” and “100” on one side and plain on the other side; supplied in:
Bottles of 30: NDC 50242-063-01

150 mg Tablets
Round, biconvex face and straight sides, white film-coated, printed in maroon with “T” and “150” on one side and plain on the other side; supplied in:
Bottles of 30: NDC 50242-064-01

Store at 25°C (77°F); excursions permitted to 15° – 30°C (59° – 86°F). See USP Controlled Room Temperature.

17 PATIENT COUNSELING INFORMATION

If the following signs or symptoms occur, patients should be advised to seek medical advice promptly *[see Warnings and Precautions (5), Adverse Reactions (6) and Dosage and Administration (2.3)]*.

- Onset or worsening of skin rash
- Severe or persistent diarrhea, nausea, anorexia, or vomiting
- Onset or worsening of unexplained shortness of breath or cough
- Eye irritation

Given that skin reactions are anticipated when taking TARCEVA, proactive intervention may include alcohol-free emollient cream and use of sunscreen or avoidance of sun exposure *[see Adverse Reactions (6.1).*] The management of rash should be discussed with the patient. This may include topical corticosteroids or antibiotics with anti-inflammatory properties. These approaches were used in the NSCLC and pancreatic pivotal clinical trials. Acne preparations with drying properties may aggravate the dry skin and erythema. Treatment of rash has not been formally studied and should be based on rash severity.

Women of childbearing potential should be advised to avoid becoming pregnant while taking TARCEVA *[see Warnings and Precautions (5.12) and Use in Specific Populations (8.1)]*.

Smokers should be advised to stop smoking while taking TARCEVA as plasma concentrations of erlotinib are reduced due to the effect of cigarette smoking *[see Clinical Pharmacology (12.3)]*.

Manufactured for:

OSI Pharmaceuticals, LLC, Farmingdale, NY 11735
an affiliate of Astellas Pharma US, Inc.

Manufactured by:

Kremers Urban Pharmaceuticals, Inc., Seymour, IN 47274

Distributed by:

Genentech USA, Inc., A Member of the Roche Group 1 DNA Way, South San Francisco, CA 94080-4990

For further information please call 1-877-TARCEVA (1-877-827-2382).

12B013-TAR