

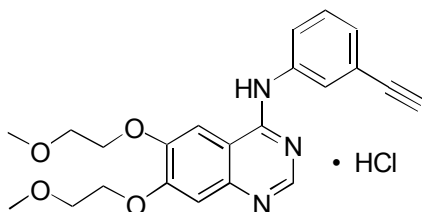
1 **PACKAGE INSERT**

2 **TARCEVA™**
3 **(erlotinib)**
4 **Tablets**

RX Only

5 **DESCRIPTION**

6 TARCEVA (erlotinib) is a Human Epidermal Growth Factor Receptor Type
7 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase inhibitor.
8 Erlotinib is a quinazolinamine with the chemical name N-(3-ethynylphenyl)-6,7-
9 bis(2-methoxyethoxy)-4-quinazolinamine. TARCEVA contains erlotinib as the
10 hydrochloride salt which has the following structural formula:



12 Erlotinib hydrochloride has the molecular formula $C_{22}H_{23}N_3O_4 \cdot HCl$ and a molecular
13 weight of 429.90. The molecule has a pK_a of 5.42 at 25°C. Erlotinib hydrochloride is
14 very slightly soluble in water, slightly soluble in methanol and practically insoluble
15 in acetonitrile, acetone, ethyl acetate and hexane.

16 Aqueous solubility of erlotinib hydrochloride is dependent on pH with increased
17 solubility at a pH of less than 5 due to protonation of the secondary amine. Over the
18 pH range of 1.4 to 9.6, maximal solubility of approximately 0.4 mg/mL occurs at a
19 pH of approximately 2.

20 TARCEVA tablets are available in three dosage strengths containing erlotinib
21 hydrochloride (27.3 mg, 109.3 mg and 163.9 mg) equivalent to 25 mg, 100 mg and
22 150 mg erlotinib and the following inactive ingredients: lactose monohydrate,
23 hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline
24 cellulose, sodium starch glycolate, sodium lauryl sulfate and titanium dioxide. The
25 tablets also contain trace amounts of color additives, including FD&C Yellow #6 (25
26 mg only) for product identification.

27 **CLINICAL PHARMACOLOGY**

28 **Mechanism of Action and Pharmacodynamics**

29 The mechanism of clinical antitumor action of erlotinib is not fully characterized.
30 Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with
31 the epidermal growth factor receptor (EGFR). Specificity of inhibition with regard to
32 other tyrosine kinase receptors has not been fully characterized. EGFR is expressed
33 on the cell surface of normal cells and cancer cells.

34 **Pharmacokinetics**

35 Erlotinib is about 60% absorbed after oral administration and its bioavailability is
36 substantially increased by food to almost 100%. Its half-life is about 36 hours and it
37 is cleared predominantly by CYP3A4 metabolism.

38 **Absorption and Distribution**

39 Bioavailability of erlotinib following a 150 mg oral dose of TARCEVA is about 60%
40 and peak plasma levels occur 4 hrs after dosing. Food increases bioavailability
41 substantially, to almost 100%.

42 Following absorption, erlotinib is approximately 93% protein bound to albumin and
43 alpha-1 acid glycoprotein (AAG). Erlotinib has an apparent volume of distribution of
44 232 liters.

45 **Metabolism and Elimination**

46 *In vitro* assays of cytochrome P450 metabolism showed that erlotinib is metabolized
47 primarily by CYP3A4 and to a lesser extent by CYP1A2, and the extrahepatic
48 isoform CYP1A1. Following a 100 mg oral dose, 91% of the dose was recovered:
49 83% in feces (1% of the dose as intact parent) and 8% in urine (0.3% of the dose as
50 intact parent).

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

56 **Special Populations**

57 *Patients with Hepatic Impairment*

58 Erlotinib is cleared predominantly by the liver. No data are currently available
59 regarding the influence of hepatic dysfunction and/or hepatic metastases on the
60 pharmacokinetics of erlotinib (see **PRECAUTIONS - Patients with Hepatic**
61 **Impairment, ADVERSE REACTIONS and DOSAGE AND**
62 **ADMINISTRATION - Dose Modifications** sections).

63 *Patients with Renal Impairment*

64 Less than 9% of a single dose is excreted in the urine. No clinical studies have been
65 conducted in patients with compromised renal function.

66 **Interactions**

67 Erlotinib is metabolized predominantly by CYP3A4, and inhibitors of CYP3A4
68 would be expected to increase exposure. Co-treatment with the potent CYP3A4
69 inhibitor ketoconazole increased erlotinib AUC by 2/3 (see **PRECAUTIONS -**
70 **Drug Interactions and DOSAGE AND ADMINISTRATION - Dose**
71 **Modifications** sections).

72 Pre- or co-treatment with the CYP3A4 inducer rifampicin increased erlotinib
73 clearance by 3-fold and reduced AUC by 2/3 (see **PRECAUTIONS - Drug**
74 **Interactions and DOSAGE AND ADMINISTRATION - Dose Modifications**
75 sections).

76 **CLINICAL STUDIES**

77 **TARCEVA as Monotherapy in Non-Small Cell Lung Cancer**
78 **(NSCLC)**

79 The efficacy and safety of TARCEVA was assessed in a randomized, double blind,
80 placebo-controlled trial in 731 patients with locally advanced or metastatic NSCLC
81 after failure of at least one chemotherapy regimen. Patients were randomized 2:1 to
82 receive TARCEVA 150 mg or placebo (488 Tarceva, 243 placebo) orally once daily
83 until disease progression or unacceptable toxicity. Study end points included overall
84 survival, response rate, and progression-free survival (PFS). Duration of response
85 was also examined. The primary endpoint was survival. The study was conducted in

86 17 countries. About 1/3 of the patients (238) had EGFR expression status
87 characterized.

88 Table 1 summarizes the demographic and disease characteristics of the study
89 population. Demographic characteristics were well balanced between the two
90 treatment groups. About two-thirds of the patients were male. Approximately one-
91 fourth had a baseline ECOG performance status (PS) of 2, and 9% had a baseline
92 ECOG PS of 3. Fifty percent of the patients had received only one prior regimen of
93 chemotherapy. About three quarters of these patients were known to have smoked at
94 some time.

95 **Table 1: Demographic and Disease Characteristics**

96

	TARCEVA (N = 488)		Placebo (N = 243)	
Characteristics	N	(%)	N	(%)
Gender				
Female	173	(35)	83	(34)
Male	315	(65)	160	(66)
Age (Years)				
<65	299	(61)	153	(63)
≥65	189	(39)	90	(37)
Race				
Caucasian	379	(78)	188	(77)
Black	18	(4)	12	(5)
Asian	63	(13)	28	(12)
Other	28	(6)	15	(6)
ECOG Performance Status at Baseline*				
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				
< 5%	320	(66)	166	(68)
5 – 10%	96	(20)	36	(15)

Characteristics	TARCEVA (N = 488)		Placebo (N = 243)	
	N	(%)	N	(%)
> 10%	52	(11)	29	(12)
Unknown	20	(4)	12	(5)
Smoking History				
Never Smoked	104	(21)	42	(17)
Current or Ex-smoker	358	(73)	187	(77)
Unknown	26	(5)	14	(6)
Histological Classification				
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 to Randomization (Months)				
<6	63	(13)	34	(14)
6 – 12	157	(32)	85	(35)
>12	268	(55)	124	(51)
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)

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100

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

101 The results of the study are shown in Table 2.

102 **Table 2: 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			

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104

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

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

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(3) Two-sided Fisher's exact test

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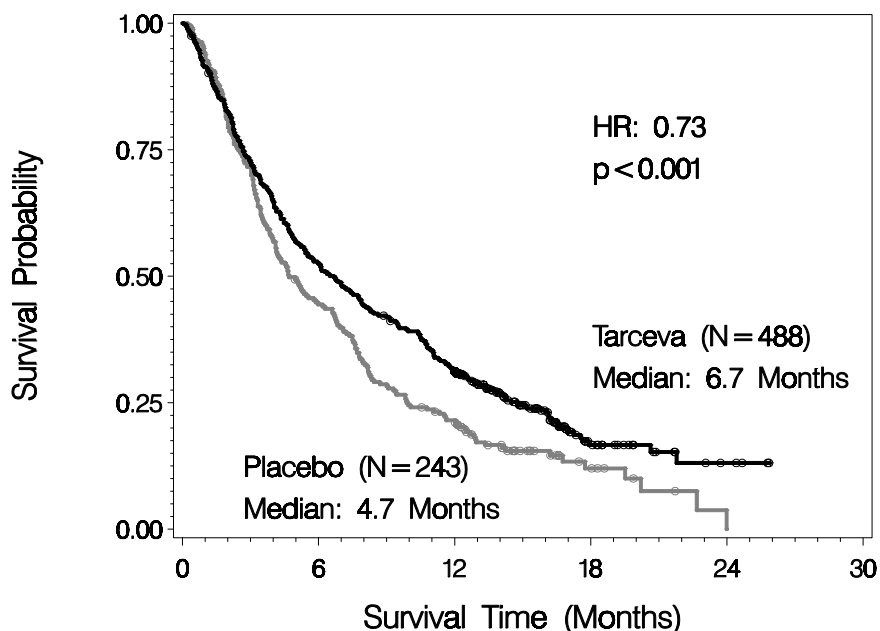
Survival was evaluated in the intent-to-treat population. Figure 1 depicts the Kaplan-Meier curves for overall survival. The primary survival and PFS analyses were two-sided Log-Rank tests stratified by ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy.

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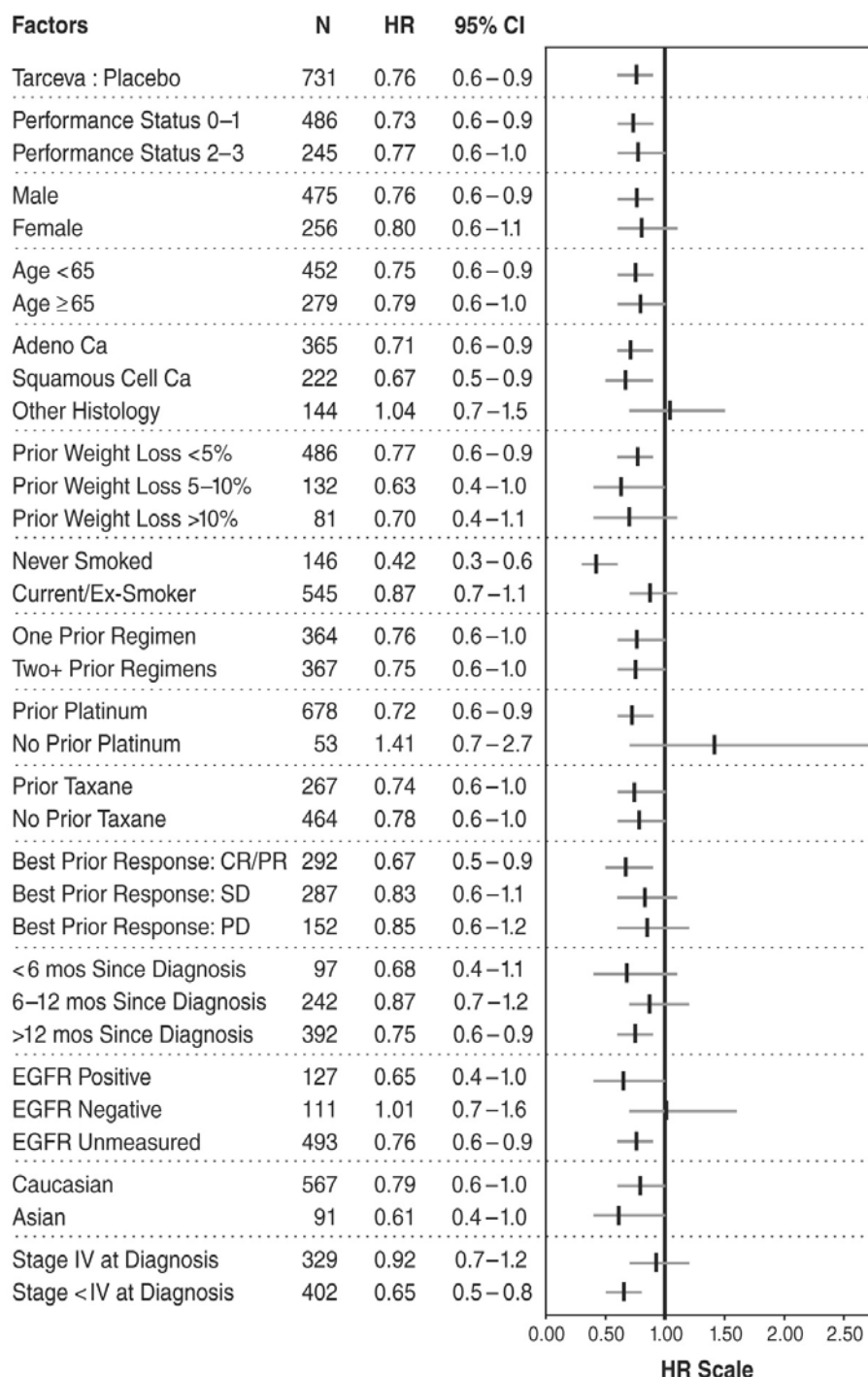
Figure 1: Kaplan–Meier Curve for Overall Survival of Patients by Treatment Group



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

121 A series of subsets of patients were examined in exploratory univariate analyses. The
122 results of these analyses are shown in Figure 2. The effect of TARCEVA on survival
123 was similar across most subsets. An apparently larger effect, however, was observed
124 in two subsets: patients with EGFR positive tumors (HR = 0.65) and patients who
125 never smoked (HR = 0.42). These subsets are considered further below.

126 **Figure 2: Survival Hazard Ratio (HR) (Tarceva : Placebo) in Subgroups**
 127 **According to Pretreatment Characteristics**



128

129 **Note:** Depicted are the univariate hazard ratio (HR) for death in the TARCEVA
 130 patients relative to the placebo patients, the 95% confidence interval (CI) for the

131 HR, and the sample size (N) in each subgroup. The hash mark on the horizontal bar
132 represents the HR, and the length of the horizontal bar represents the 95%
133 confidence interval. A hash mark to the left of the vertical line corresponds to a HR
134 that is less than 1.00, which indicates that survival is better in the TARCEVA arm
135 compared with the placebo arm in that subgroup.

136

137 **Relation of Results to EGFR Protein Expression Status (as**
138 **Determined by Immunohistochemistry)**

139 Analysis of the impact of EGFR expression status on the treatment effect on clinical
140 outcome is limited because EGFR status is known for only 238 study patients (33%).
141 EGFR status was ascertained for patients who already had tissue samples prior to
142 study enrollment. However, the survival in the EGFR tested population, and the
143 effect of TARCEVA were almost identical to that in the entire study population,
144 suggesting that the tested population was a representative sample. A positive EGFR
145 expression status was defined as having at least 10% of cells staining for EGFR in
146 contrast to the 1% cut-off specified in the DAKO EGFR pharmDx™ kit instructions.
147 The use of the pharmDx kit has not been validated for use in non-small cell lung
148 cancer.

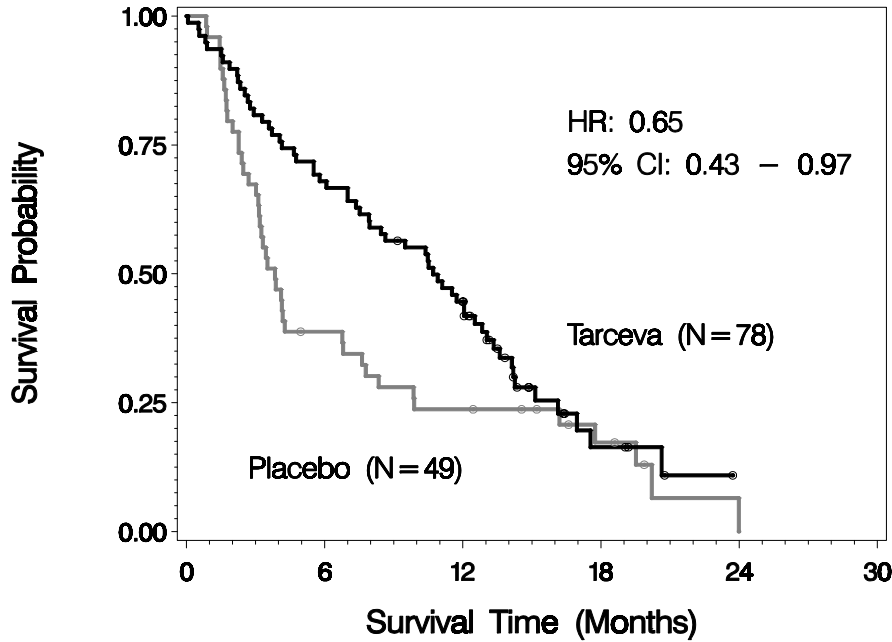
149 TARCEVA prolonged survival in the EGFR positive subgroup (N = 127; HR = 0.65;
150 95% CI = 0.43 – 0.97)(Figure 3) and the subgroup whose EGFR status was
151 unmeasured (N = 493; HR = 0.76; 95% CI = 0.61 – 0.93)(Figure 5), but did not
152 appear to have an effect on survival in the EGFR negative subgroup (N = 111; HR =
153 1.01; 95% CI = 0.65 – 1.57)(Figure 4). However, the confidence intervals for the
154 EGFR positive, negative and unmeasured subgroups are wide and overlap, so that a
155 survival benefit due to TARCEVA in the EGFR negative subgroup cannot be
156 excluded.

157 For the subgroup of patients who never smoked, EGFR status also appeared to be
158 predictive of TARCEVA survival benefit. Patients who never smoked and were
159 EGFR positive had a large TARCEVA survival benefit (N = 30; HR = 0.27; 95% CI
160 = 0.11 – 0.67). There were too few EGFR negative patients who never smoked to
161 reach a conclusion.

162 Tumor responses were observed in all EGFR subgroups: 11.6% in the EGFR positive
163 subgroup, 9.5% in the EGFR unmeasured subgroup and 3.2% in the EGFR negative

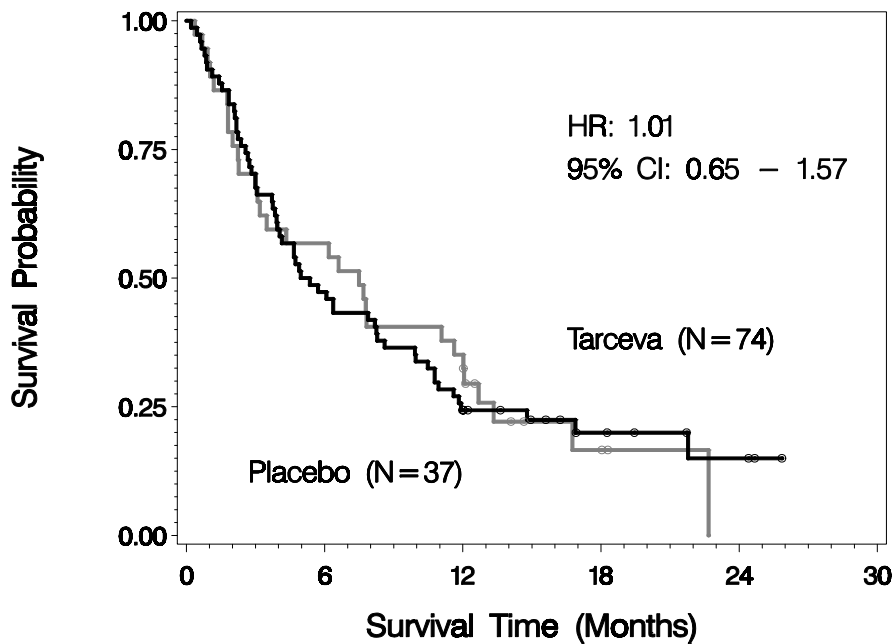
164 subgroup. An improvement in progression free survival was demonstrated in the
165 EGFR positive subgroup (HR = 0.49; 95% CI = 0.33 – 0.72), the EGFR unmeasured
166 subgroup (HR = 0.56; 95% CI = 0.46 – 0.70), and less certain in the EGFR negative
167 subgroup (HR = 0.91; 95% CI = 0.59 – 1.39).

Figure 3: Survival in EGFR Positive Patients



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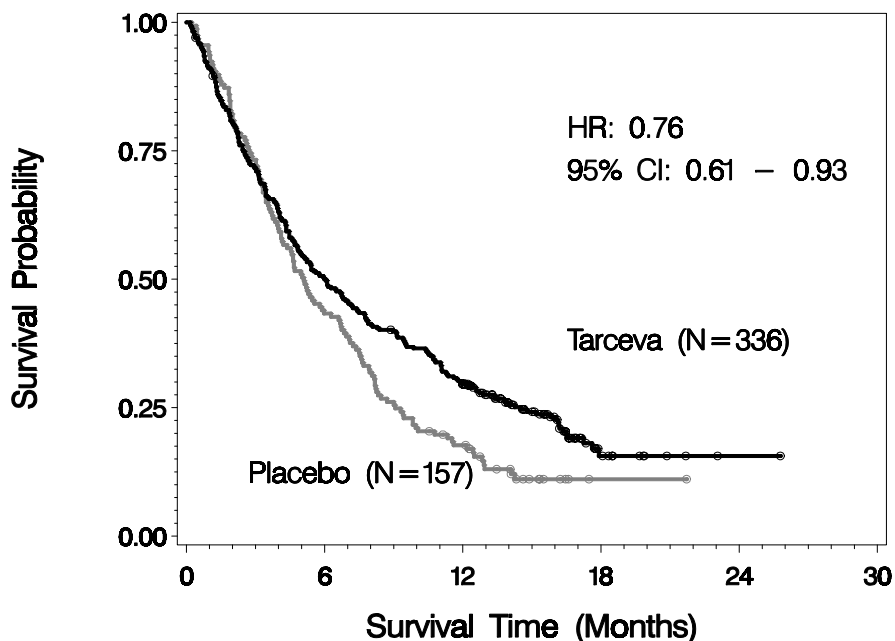
Figure 4: Survival in EGFR Negative Patients



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Figure 5: Survival in EGFR Unmeasured Patients



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172 **TARCEVA Administered Concurrently with Chemotherapy in NSCLC**

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

178 **INDICATIONS AND USAGE**

179 TARCEVA is indicated for the treatment of patients with locally advanced or
180 metastatic non-small cell lung cancer after failure of at least one prior chemotherapy
181 regimen.

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

187 **CONTRAINDICATIONS**

188 None.

189 **WARNINGS**

190 **Pulmonary Toxicity**

191 There have been infrequent reports of serious Interstitial Lung Disease (ILD),
192 including fatalities, in patients receiving TARCEVA for treatment of NSCLC or
193 other advanced solid tumors. In the randomized single-agent study (see **CLINICAL**
194 **STUDIES** section), the incidence of ILD (0.8%) was the same in both the placebo
195 and TARCEVA groups. The overall incidence in TARCEVA-treated patients from
196 all studies (including uncontrolled studies and studies with concurrent
197 chemotherapy) was approximately 0.6%. Reported diagnoses in patients suspected of
198 having ILD included pneumonitis, interstitial pneumonia, interstitial lung disease,
199 obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome
200 and lung infiltration. Symptoms started from 5 days to more than 9 months (median
201 47 days) after initiating TARCEVA therapy. Most of the cases were associated with
202 confounding or contributing factors such as concomitant/prior chemotherapy, prior
203 radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or
204 pulmonary infections.

205 In the event of acute onset of new or progressive, unexplained pulmonary symptoms
206 such as dyspnea, cough, and fever, TARCEVA therapy should be interrupted
207 pending diagnostic evaluation. If ILD is diagnosed, TARCEVA should be
208 discontinued and appropriate treatment instituted as necessary (see **ADVERSE**
209 **REACTIONS** and **DOSAGE AND ADMINISTRATION - Dose Modifications**
210 sections).

211 **Pregnancy Category D**

212 Erlotinib has been shown to cause maternal toxicity with associated embryo/fetal
213 lethality and abortion in rabbits when given at doses that result in plasma drug
214 concentrations of approximately 3 times those in humans (AUCs at 150 mg daily
215 dose). When given during the period of organogenesis to achieve plasma drug
216 concentrations approximately equal to those in humans, based on AUC, there was no
217 increased incidence of embryo/fetal lethality or abortion in rabbits or rats. However,
218 female rats treated with 30 mg/m²/day or 60 mg/m²/day (0.3 or 0.7 times the clinical

219 dose, on a mg/m² basis) of erlotinib prior to mating through the first week of
220 pregnancy had an increase in early resorptions which resulted in a decrease in the
221 number of live fetuses.

222 No teratogenic effects were observed in rabbits or rats.

223 There are no adequate and well-controlled studies in pregnant women using
224 TARCEVA. Women of childbearing potential should be advised to avoid pregnancy
225 while on TARCEVA. Adequate contraceptive methods should be used during
226 therapy, and for at least 2 weeks after completing therapy. Treatment should only be
227 continued in pregnant women if the potential benefit to the mother outweighs the risk
228 to the fetus. If TARCEVA is used during pregnancy, the patient should be apprised
229 of the potential hazard to the fetus or potential risk for loss of the pregnancy.

230 **PRECAUTIONS**

231 **Drug Interactions**

232 Co-treatment with the potent CYP3A4 inhibitor ketoconazole increases erlotinib
233 AUC by 2/3. Caution should be used when administering or taking TARCEVA with
234 ketoconazole and other strong CYP3A4 inhibitors such as atazanavir,
235 clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir,
236 saquinavir, telithromycin, troleandomycin (TAO), and voriconazole (see **DOSAGE**
237 **AND ADMINISTRATION - Dose Modifications** section).

238 Pre-treatment with the CYP3A4 inducer rifampicin decreased erlotinib AUC by
239 about 2/3. Alternate treatments lacking CYP3A4 inducing activity should be
240 considered. If an alternative treatment is unavailable, a TARCEVA dose greater than
241 150 mg should be considered. If the TARCEVA dose is adjusted upward, the dose
242 will need to be reduced upon discontinuation of rifampicin or other inducers. Other
243 CYP3A4 inducers include rifabutin, rifapentin, phenytoin, carbamazepine,
244 phenobarbital and St. John's Wort (see **DOSAGE AND ADMINISTRATION -**
245 **Dose Modifications** section).

246 **Hepatotoxicity**

247 Asymptomatic increases in liver transaminases have been observed in TARCEVA
248 treated patients; therefore, periodic liver function testing (transaminases, bilirubin,
249 and alkaline phosphatase) should be considered. Dose reduction or interruption of

250 TARCEVA should be considered if changes in liver function are severe (see
251 **ADVERSE REACTIONS** section).

252 **Patients with Hepatic Impairment**

253 *In vitro* and *in vivo* evidence suggest that erlotinib is cleared primarily by the liver.
254 Therefore, erlotinib exposure may be increased in patients with hepatic dysfunction
255 (see **CLINICAL PHARMACOLOGY - Special Populations - Patients with**
256 **Hepatic Impairment** and **DOSAGE AND ADMINISTRATION - Dose**
257 **Modification** sections).

258 **Elevated International Normalized Ratio and Potential Bleeding**

259 International Normalized Ratio (INR) elevations, and infrequent reports of bleeding
260 events including gastrointestinal bleeding have been reported in clinical studies,
261 some associated with concomitant warfarin administration. Patients taking warfarin
262 or other coumarin-derivative anticoagulants should be monitored regularly for
263 changes in prothrombin time or INR (see **ADVERSE REACTIONS** section).

264 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

265 Erlotinib has not been tested for carcinogenicity.

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

270 **Pregnancy**

271 **Pregnancy Category D** (see **WARNINGS** and **PRECAUTIONS - Information**
272 **for Patients** sections).

273 **Nursing Mothers**

274 It is not known whether erlotinib is excreted in human milk. Because many drugs are
275 excreted in human milk and because the effects of TARCEVA on infants have not
276 been studied, women should be advised against breast-feeding while receiving
277 TARCEVA therapy.

278 **Pediatric Use**

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

281 **Geriatric Use**

282 Of the total number of patients participating in the randomized trial, 62% were less
283 than 65 years of age, and 38% of patients were aged 65 years or older. The survival
284 benefit was maintained across both age groups (see **CLINICAL STUDIES** section).
285 No meaningful differences in safety or pharmacokinetics were observed between
286 younger and older patients. Therefore, no dosage adjustments are recommended in
287 elderly patients.

288 **Information for Patients**

289 If the following signs or symptoms occur, patients should seek medical advice
290 promptly (see **WARNINGS, ADVERSE REACTIONS** and **DOSAGE AND**
291 **ADMINISTRATION - Dose Modification** sections).

- 292 • Severe or persistent diarrhea, nausea, anorexia, or vomiting
293 • Onset or worsening of unexplained shortness of breath or cough
294 • Eye irritation

295 Women of childbearing potential should be advised to avoid becoming pregnant
296 while taking TARCEVA (see **WARNINGS - Pregnancy Category D** section).

297 **ADVERSE REACTIONS**

298 Safety evaluation of TARCEVA is based on 856 cancer patients who received
299 TARCEVA as monotherapy and 1228 patients who received TARCEVA
300 concurrently with chemotherapy. Adverse events, regardless of causality, that
301 occurred in at least 10% of patients treated with TARCEVA and at least 3% more
302 often than in the placebo group in the randomized trial are summarized by NCI-CTC
303 (version 2.0) Grade in Table 3.

304 There have been reports of serious ILD, including fatalities, in patients receiving
305 TARCEVA for treatment of NSCLC or other advanced solid tumors (see
306 **WARNINGS - Pulmonary Toxicity**, and **DOSAGE AND ADMINISTRATION -**
307 **Dose Modifications** sections).

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

314 **Table 3: Adverse Events Occurring in ≥10% of TARCEVA-treated Patients**
315 **(2:1 Randomization of TARCEVA to Placebo)**

NCI CTC Grade MedDRA Preferred Term	TARCEVA N = 485			Placebo N = 242		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	%	%	%	%	%	%
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

316 Liver function test abnormalities (including elevated alanine aminotransferase
317 (ALT), aspartate aminotransferase (AST) and bilirubin) have been observed. These
318 elevations were mainly transient or associated with liver metastases. Grade 2 (>2.5 –
319 5.0 x ULN) ALT elevations occurred in 4% and <1% of TARCEVA and placebo
320 treated patients, respectively. Grade 3 (> 5.0 – 20.0 x ULN) elevations were not
321 observed in TARCEVA-treated patients. Dose reduction or interruption of

322 TARCEVA should be considered if changes in liver function are severe (see
323 **DOSAGE AND ADMINISTRATION - Dose Modification** section).

324 Infrequent cases of gastrointestinal bleeding have been reported in clinical studies,
325 some associated with concomitant warfarin administration (see **PRECAUTIONS -**
326 **Elevated International Normalized Ratio and Potential Bleeding** section) and
327 some with concomitant NSAID administration.

328 NCI CTC grade 3 conjunctivitis and keratitis have been reported infrequently in
329 patients receiving TARCEVA therapy. Corneal ulcerations may also occur (see
330 **PRECAUTIONS - Information for Patients** section).

331 In general, no notable differences in the safety of TARCEVA could be discerned
332 between females or males and between patients younger or older than the age of 65
333 years. The safety of TARCEVA appears similar in Caucasian and Asian patients (see
334 **PRECAUTIONS - Geriatric Use** section).

335 **OVERDOSAGE**

336 Single oral doses of TARCEVA up to 1,000 mg in healthy subjects, and up to 1,600
337 mg in cancer patients have been tolerated. Repeated twice-daily doses of 200 mg in
338 healthy subjects were poorly tolerated after only a few days of dosing. Based on the
339 data from these studies, an unacceptable incidence of severe adverse events, such as
340 diarrhea, rash, and liver transaminase elevation, may occur above the recommended
341 dose of 150 mg daily. In case of suspected overdose, TARCEVA should be withheld
342 and symptomatic treatment instituted.

343 **DOSAGE AND ADMINISTRATION**

344 The recommended daily dose of TARCEVA is 150 mg taken at least one hour before
345 or two hours after the ingestion of food. Treatment should continue until disease
346 progression or unacceptable toxicity occurs. There is no evidence that treatment
347 beyond progression is beneficial.

348 **Dose Modifications**

349 In patients who develop an acute onset of new or progressive pulmonary symptoms,
350 such as dyspnea, cough or fever, treatment with TARCEVA should be interrupted
351 pending diagnostic evaluation. If ILD is diagnosed, TARCEVA should be

352 discontinued and appropriate treatment instituted as necessary (see **WARNINGS –**
353 **Pulmonary Toxicity** section).

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

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

360 In patients who are being concomitantly treated with a strong CYP3A4 inhibitor
361 such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole,
362 nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO),
363 or voriconazole, a dose reduction should be considered should severe adverse
364 reactions occur.

365 Pre-treatment with the CYP3A4 inducer rifampicin decreased erlotinib AUC by
366 about 2/3. Alternate treatments lacking CYP3A4 inducing activity should be
367 considered. If an alternative treatment is unavailable, a TARCEVA dose greater than
368 150 mg should be considered. If the TARCEVA dose is adjusted upward, the dose
369 will need to be reduced upon discontinuation of rifampicin or other inducers. Other
370 CYP3A4 inducers include rifabutin, rifapentin, phenytoin, carbamazepine,
371 phenobarbital and St. John's Wort. These too should be avoided if possible (see
372 **PRECAUTIONS - Drug Interactions** section).

373 Erlotinib is eliminated by hepatic metabolism and biliary excretion. Therefore,
374 caution should be used when administering TARCEVA to patients with hepatic
375 impairment. Dose reduction or interruption of TARCEVA should be considered
376 should severe adverse reactions occur (see **CLINICAL PHARMACOLOGY -**
377 **Special Populations – Patients With Hepatic Impairment, PRECAUTIONS -**
378 **Patients With Hepatic Impairment, and ADVERSE REACTIONS** sections).

379 **HOW SUPPLIED**

380 The 25 mg, 100 mg and 150 mg strengths are supplied as white film-coated tablets
381 for daily oral administration.

382 TARCEVA™ (erlotinib) Tablets, 25 mg: Round, biconvex face and straight sides,
383 white film-coated, printed in orange with a “T” and “25” on one side and plain on the
384 other side. Supplied in bottles of 30 tablets (NDC 50242-062-01).

385 TARCEVA™ (erlotinib) Tablets, 100 mg: Round, biconvex face and straight sides,
386 white film-coated, printed in gray with “T” and “100” on one side and plain on the
387 other side. Supplied in bottles of 30 tablets (NDC 50242-063-01).

388 TARCEVA™ (erlotinib) Tablets, 150 mg: Round, biconvex face and straight sides,
389 white film-coated, printed in maroon with “T” and “150” on one side and plain on
390 the other side. Supplied in bottles of 30 tablets (NDC 50242-064-01).

391 **STORAGE**

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

Manufactured for:

OSI Pharmaceuticals Inc., Melville, NY 11747

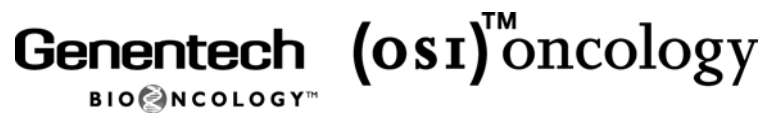
Manufactured by:

Schwarz Pharma Manufacturing, Seymour, IN 47274

Distributed by:

Genentech Inc., 1 DNA Way, South San Francisco, CA 94080-4990

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



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/s/

Robert Temple
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