

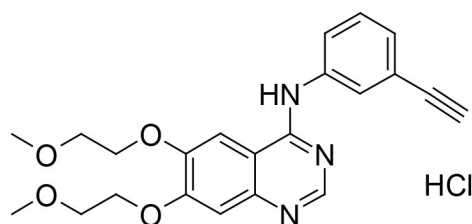
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## NAME OF THE MEDICINE

### TARCEVA®

Erlotinib hydrochloride

CAS Registry Number: 183319-69-9



## DESCRIPTION

TARCEVA (erlotinib hydrochloride) is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR, also known as HER1) tyrosine kinase inhibitor. Erlotinib, the active ingredient of TARCEVA, is a quinazolinamine with the chemical name N-(3-ethynylphenyl)- 6,7- bis(2- methoxyethoxy)- 4- quinazolinamine.

Erlotinib hydrochloride has the molecular formula  $C_{22}H_{23}N_3O_4 \cdot HCl$  and a molecular mass of 429.9. The molecule has a  $pK_a$  of 5.42 at 25°C. Erlotinib hydrochloride is an off-white to pale yellow powder, it is sparingly soluble in water, slightly soluble in methanol and practically insoluble in acetonitrile, acetone, ethyl acetate and hexane.

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

TARCEVA tablets are available in 3 dosage strengths containing erlotinib hydrochloride equivalent to 25 mg, 100 mg or 150 mg of erlotinib and the following inactive ingredients: lactose, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate and magnesium stearate. The film coating contains hypromellose, hydroxypropylcellulose, macrogol 400 and titanium dioxide. The printing ink contains iron oxide yellow CI 77492 (25, 100 and 150 mg tablets), iron oxide black CI77499 (100 and 150 mg tablets) and iron oxide red CI77491 (150 mg tablets).

## PHARMACOLOGY

### Pharmacodynamics

Erlotinib potently inhibits the intracellular phosphorylation of HER1/EGFR tyrosine kinase with nanomolar potency; HER1/EGFR is expressed on the cell surface of normal cells and cancer cells

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of epithelial origin. However, the mechanism of antitumour action of erlotinib is not fully characterised. Erlotinib has been demonstrated to inhibit proliferation and/or induce apoptosis in human cancer cell lines *in vitro* and to inhibit the growth of a variety of human tumour xenografts in nude mice. Specificity of inhibition with regard to other tyrosine kinase receptors has not been fully characterised.

## Pharmacokinetics

**Absorption:** Oral erlotinib is well absorbed and has an extended absorption phase, with mean peak plasma levels occurring at approximately 4 hours after oral dosing. A study in normal healthy volunteers provided an estimate of bioavailability of 59%. The exposure after an oral dose may be increased by food.

Following absorption, erlotinib is highly bound in blood, with approximately 95% bound to blood components, primarily to plasma proteins (i.e. albumin and alpha-1 acid glycoprotein [AAG]).

**Distribution:** Erlotinib has a mean apparent volume of distribution of 232 L and distributes into tumour tissue of humans. In a study of 4 patients (3 with non-small cell lung cancer [NSCLC] and 1 with laryngeal cancer) receiving 150 mg daily oral doses of TARCEVA, tumour samples from surgical excisions on day 9 of treatment revealed tumour concentrations of erlotinib that averaged 1 185 ng/g of tissue. This corresponded to an overall average of 63% of the steady state observed peak plasma concentrations. The primary active metabolites were present in tumours at concentrations averaging 160 ng/g tissue, which corresponded to an overall average of 113% of the observed steady state peak plasma concentrations. Tissue distribution studies using whole body autoradiography following oral administration of [<sup>14</sup>C] labelled erlotinib in athymic nude mice with HN5 (head and neck carcinoma) tumour xenografts have shown rapid and extensive tissue distribution with maximum concentrations of radiolabeled drug in tumours (approximately 73% of that in plasma) and most other tissues observed to coincide with the peak plasma concentration.

**Metabolism:** Erlotinib is metabolised by the hepatic cytochromes in humans, primarily CYP3A4/CYP3A5 and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung and CYP1B1 in tumour tissue potentially contribute to the metabolic clearance of erlotinib. *In vitro* studies indicate approximately 80 – 95% of erlotinib metabolism is by the CYP3A4 enzyme. There are 3 main metabolic pathways identified: 1) O-demethylation of either side chain or both, followed by oxidation to the carboxylic acids; 2) oxidation of the acetylene moiety followed by hydrolysis to the aryl carboxylic acid; and 3) aromatic hydroxylation of the phenyl-acetylene moiety. The primary metabolites of erlotinib produced by O-demethylation of either side chain have comparable potency to erlotinib in preclinical *in vitro* assays. They are present in plasma at levels that are < 10% of erlotinib and display similar pharmacokinetics to erlotinib. The metabolites and trace amounts of erlotinib are excreted predominantly via the faeces (> 90%), with renal elimination accounting for only a small amount of an oral dose.

**Elimination:** A population pharmacokinetic analysis in 591 patients receiving single agent TARCEVA (252 patients from Phase II studies A248-101, A248-1003, A248-1007 and OSI2288g; 339 patients from Phase III study BR.21) show a mean apparent clearance of 4.47 L/hour with a median half-life of 36.2 hours. Therefore, the time to reach steady state plasma concentration would be expected to occur in approximately 7 – 8 days. No significant relationships between predicted apparent clearance and patient age, body weight, gender and ethnicity were observed.

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Patient factors, which correlate with erlotinib pharmacokinetics, are serum total bilirubin, AAG and current smoking. Increased serum concentrations of total bilirubin and AAG were associated with a slower rate of erlotinib clearance, however, smokers had a higher rate of erlotinib clearance.

A second population pharmacokinetic analysis was conducted incorporating 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.

Following a 150 mg oral dose of TARCEVA (591 patients – see above), at steady state, the median time to reach maximum plasma concentration is approximately 4 hours with median maximum plasma concentration achieved of 1 995 ng/mL. Prior to the next dose at 24 hours, the median minimum plasma concentration is 1 238 ng/mL. Median AUC achieved during the dosing interval at steady state is 41.3 µg.h/mL.

### **Pharmacokinetics in Special Populations**

**Hepatic impairment:** Erlotinib is primarily cleared by the liver. Erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh score 7 – 9) compared with patients with adequate hepatic function.

The pharmacokinetics of erlotinib and its o-demethylated metabolites OSI-420 and OSI-413 were assessed in 36 patients with advanced solid tumours after a single 150 mg oral dose. Twenty-one patients had adequate hepatic function (total serum bilirubin ≤ upper limit of normal (ULN) and AST/ALT ≤ 1.5 x ULN) and 15 had moderate hepatic impairment (Child-Pugh score 7 – 9).

Erlotinib and metabolite exposures were similar in the two groups, with geometric mean AUCs of 29 and 27 µg.h/mL for erlotinib in adequate and impaired hepatic function respectively and 2.0 and 2.4 µg.h/mL for metabolites respectively. However, the confidence intervals of the ratios of the AUCs were wide, so it could not be concluded that exposures were equivalent. The  $C_{max}$  of erlotinib was significantly lower in moderate hepatic impaired patients compared with those with adequate hepatic function consistent with delayed  $T_{max}$ . The differences in  $C_{max}$  and  $T_{max}$  are not clinically significant.

**Renal impairment:** Erlotinib and its metabolites are not significantly excreted by the kidneys (less than 9% of a single dose is excreted in the urine). No clinical studies have been conducted in patients with compromised renal function.

**Smokers:** A pharmacokinetic study in healthy non-smoking subjects and healthy subjects who currently smoke has shown that cigarette smoking leads to increased clearance of, and decreased exposure to, erlotinib. After a single 150 mg dose of erlotinib, the  $AUC_{0-\infty}$  in smokers was about 1/3 of that in never/former smokers ( $n = 16$  in each of the smoker and never/former smoker arms). This reduced exposure in smokers is presumably due to induction of CYP1A1 in the lungs and CYP1A2 in the liver.

In the pivotal Phase III NSCLC trial (see CLINICAL TRIALS), smokers achieved a median erlotinib steady state trough plasma concentration of 0.65 µg/mL ( $n = 16$ ) which was

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approximately 2-fold less than the former smokers or patients who had never smoked (1.28 µg/mL,  $n = 108$ ). This effect was accompanied by a 24% increase in apparent erlotinib plasma clearance.

In a Phase I dose escalation study in NSCLC patients who smoked, pharmacokinetic analyses at steady state indicated a dose proportional increase in erlotinib exposure when the TARCEVA dose was increased from 150 mg to the maximum tolerated dose of 300 mg. Median steady state trough plasma concentration at a 300 mg dose in smokers in this study was 1.22 µg/mL ( $n = 17$ ) compared with 0.38 µg/mL ( $n = 15$ ) at 150 mg. (see DOSAGE AND ADMINISTRATION; Special Dosage Instructions)

## CLINICAL TRIALS

### Non-Small Cell Lung Cancer (NSCLC) – TARCEVA Monotherapy

#### *First-line therapy for patients with Epidermal Growth Factor Receptor (EGFR) activating mutations*

The efficacy of TARCEVA in first-line treatment of patients with EGFR activating mutations in NSCLC was demonstrated in a phase III, randomised, open-label trial (ML20650, EURTAC). This study was conducted in Caucasian patients with metastatic or locally advanced NSCLC (stage IIIB and IV) who have not received previous chemotherapy or any systemic antitumour therapy for their advanced disease and who present mutations in the tyrosine kinase domain of the EGFR (exon 19 deletion or exon 21 mutation). Patients were randomised 1:1 to receive TARCEVA 150 mg orally once daily or platinum based doublet chemotherapy.

The primary endpoint of investigator assessed progression free survival (PFS), was determined at a pre-planned interim analysis ( $n=153$ , hazard ratio (HR) = 0.42, 95 % CI, 0.27 to 0.64;  $p<0.0001$  for the TARCEVA group ( $n=77$ ) relative to the chemotherapy group ( $n=76$ )). A 58% reduction in the risk of disease progression or death was observed. In the TARCEVA versus chemotherapy arms, median PFS was 9.4 and 5.2 months, respectively. The median duration of follow-up was 14.3 months for erlotinib patients and 10.7 months for chemotherapy patients. Objective response rate (ORR) was 54.5 % and 10.5%, respectively. PFS results were confirmed by an independent review of the scans, median PFS was 10.4 months in the TARCEVA group compared with 5.4 months in the chemotherapy group (HR=0.47, 95 % CI, 0.28 to 0.78;  $p=0.003$ ). The overall survival (OS) data were immature at the time of interim analysis (HR= 0.80, 95 % CI, 0.47 to 1.37,  $p=0.4170$ ).

#### *First-line maintenance therapy*

The efficacy and safety of TARCEVA as first-line maintenance therapy of NSCLC was demonstrated in a randomised, double-blind, placebo-controlled trial (BO18192). This study was conducted in 889 patients with locally advanced or metastatic NSCLC who did not progress during 4 cycles of platinum-based doublet chemotherapy. Patients were randomised 1:1 to receive TARCEVA 150 mg or placebo orally once daily. The co-primary end-point of the study was progression free survival (PFS) in all patients and in patients with an EGFR IHC positive tumour. Baseline demographic and disease characteristics were well balanced between the two treatment arms.

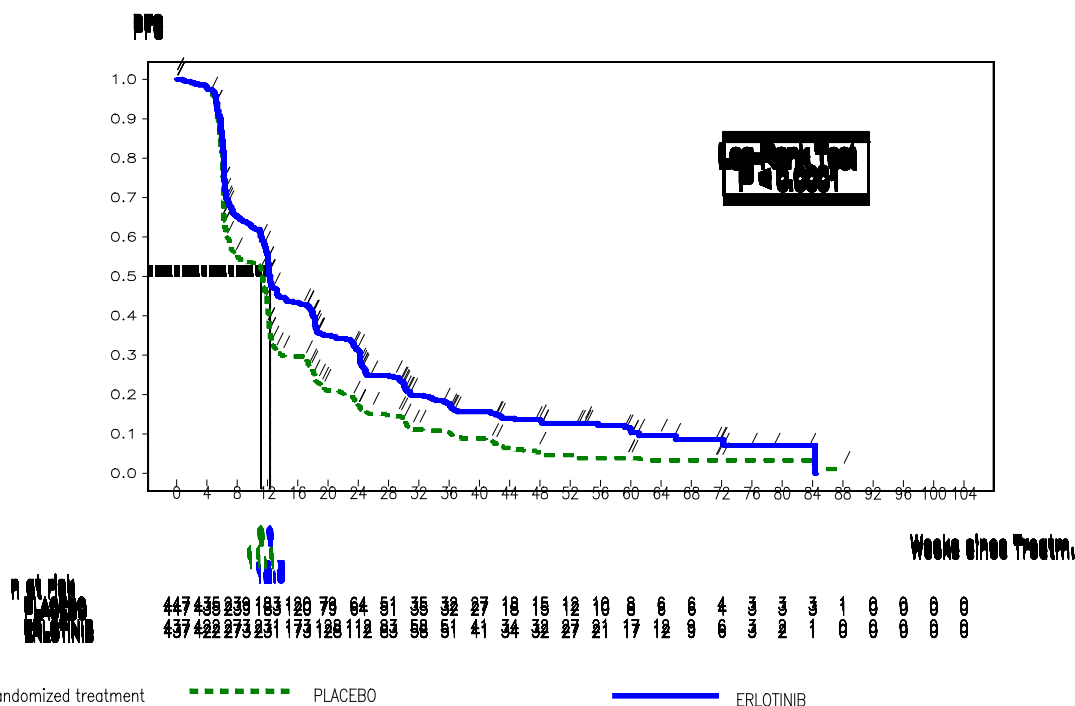
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Table 1 and Figure 1 show the results of the primary PFS analysis in the intent-to-treat (ITT) population (data cut-off 17 May 2008).

**Table 1: Study BO18192 Efficacy Results (ITT population)**

	<b>TARCEVA 150 mg</b> <b>(n = 438)</b>	<b>Placebo</b> <b>(n = 451)</b>
<b>Hazard ratio</b> <b>(95% CI)</b>	0.71 ( $p < 0.0001$ ) (0.62 – 0.82)	
<b>Median PFS (months)</b>	2.8	2.6
<b>Mean PFS (months)</b> <b>(range)</b>	5.2 (0.02 – 19.4)	3.7 (0.02 – 20.3)
<b>6 months PFS rate</b>	25%	15%
<b>Disease Control Rate</b> <b>(CR, PR, SD&gt;12 weeks)</b>	40.8%	27.4%

**Figure 1: Kaplan-Meier Curve for PFS of Patients by Treatment Group in Study BO18192**



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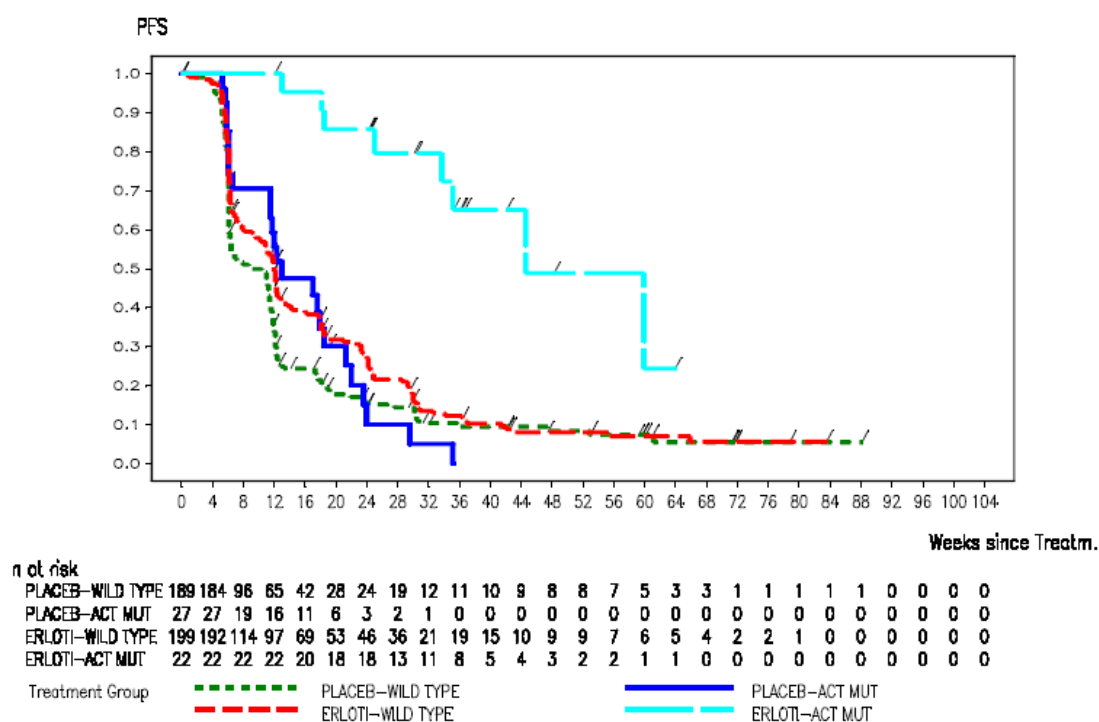
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The co-primary PFS analysis in patients with an EGFR IHC positive tumour was similar, with a hazard ratio (HR) of 0.69 (95% CI: 0.58 – 0.82;  $p < 0.0001$ ). The median PFS was 2.8 months in the TARCEVA group (range 0.02 – 18.1 months) compared with 2.6 months in the placebo group (range 0.02 – 20.3 months). The percentage of patients without progression at 6 months was 27% and 16%, respectively.

The PFS increase was consistent across subgroups (independent of EGFR IHC, FISH, K-ras mutation biomarker subgroup status) with the exception of patients with activating EGFR mutations (n=49) where the benefit was greater: HR = 0.10, 95% CI [0.04, 0.25] (Figure 2). In patients with EGFR wild-type tumours (n=388), the PFS HR was 0.78, 95% CI [0.63, 0.96].

Quality of life measurements suggested a similar effect from TARCEVA compared with placebo.

**Figure 2: Kaplan-Meier Curve of PFS by Study Treatment and EGFR Mutation Status (Activating Mutation and Wild Type)**



The benefit in PFS translated into statistically significant and clinically relevant benefit in overall survival (OS) (secondary end-point, HR = 0.81, see Table 2).

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**Table 2: Study BO18192 Efficacy Results, Overall Survival (ITT population)**

	<b><u>TARCEVA 150 mg</u></b> <b>(n = 438)</b>	<b><u>Placebo</u></b> <b>(n = 451)</b>
<b>Hazard ratio</b> <b>(95% CI)</b>	0.81 ( $p = 0.0088$ ) (0.70 – 0.95)	
<b>Median Overall Survival</b>	12.0 months	11.0 months

In the EGFR IHC positive population the median OS was 11.0 months in the placebo group and 12.8 months in the TARCEVA group (HR 0.77; 95% CI: 0.64 – 0.93;  $p = 0.0063$ ).

An updated analysis of the EGFR mutation subgroup data confirmed the significant benefit of TARCEVA in patients with EGFR mutation positive tumours showing a median 7.6 months increase in PFS. The OS data were immature. In patients with EGFR wild-type tumours, the median increase in PFS and OS was approximately one month (Table 3).

**Table 3: Study BO18192 – EGFR Mutation Subgroup Data – 17 May 2009 cut-off**

	<b>TARCEVA</b>	<b>Placebo</b>	<b>Hazard Ratio [95% CI]</b> <b>Log-Rank p</b>
<b>EGFR Mutation +ve</b>	<b><i>n = 22</i></b>	<b><i>n = 27</i></b>	
<b>PFS median</b> <b>(months)</b>	10.6	3.0	0.23 [0.12, 0.45] $p < 0.0001$
<b>OS median</b> <b>(months)</b>	NR	23.8	0.83 [0.34, 2.02] $p = 0.68$
<b>EGFR Wild-Type</b>	<b><i>n = 199</i></b>	<b><i>n = 189</i></b>	
<b>PFS median</b> <b>(months)</b>	2.8	2.0	0.78 [0.64, 0.96] $p = 0.02$
<b>OS median</b> <b>(months)</b>	11.3	10.2	0.77 [0.61, 0.97] $p = 0.02$

PFS: Progression-Free Survival, OS: Overall Survival. NR: Not Reached.

### ***Second-line and third-line therapy***

The efficacy and safety of TARCEVA in second and third line therapy of NSCLC was demonstrated in a randomised, double-blind, placebo-controlled trial (Study BR.21). This study



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was conducted in 17 countries, in 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen. Patients, following disease progression, were randomised 2:1 to receive TARCEVA 150 mg ( $n = 488$ ) or placebo ( $n = 243$ ) orally once daily. Study endpoints included overall survival, time to deterioration of lung cancer-related symptoms (cough, dyspnoea and pain), response rate, duration of response, progression-free survival (PFS) and safety. The primary end-point was survival.

Patients were not selected for HER1/EGFR status, gender, race, smoking history or histologic classification. Demographic characteristics were well balanced between the two treatment groups (see Table 4). Approximately two-thirds of the patients were male and approximately one-third had a baseline ECOG performance status (PS) of 2 and 9% had a baseline ECOG PS of 3. Ninety-three percent and 92% of all patients in the TARCEVA and placebo groups respectively, had received a prior platinum-containing regimen and 36% and 37% of all patients respectively, had received a prior taxane therapy. Fifty percent of the patients had received only one prior regimen of chemotherapy.

**Table 4: Study BR.21- Demographic and Disease Characteristics**

Characteristics	TARCEVA $n = 488$		Placebo $n = 243$	
	$n$	(%)	$n$	(%)
Gender				
Female	173	(35)	83	(34)
Male	315	(65)	160	(66)
Age (years)				
< 65	299	(61)	153	(63)
≥ 65	189	(39)	90	(37)
ECOG Performance Status				
0	64	(13)	34	(14)
1	256	(52)	132	(54)
2	126	(26)	56	(23)
3	42	(9)	21	(9)
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)
Number of prior regimens				
1	243	(50)	121	(50)
2	238	(49)	119	(49)
3	7	(1)	3	(1)

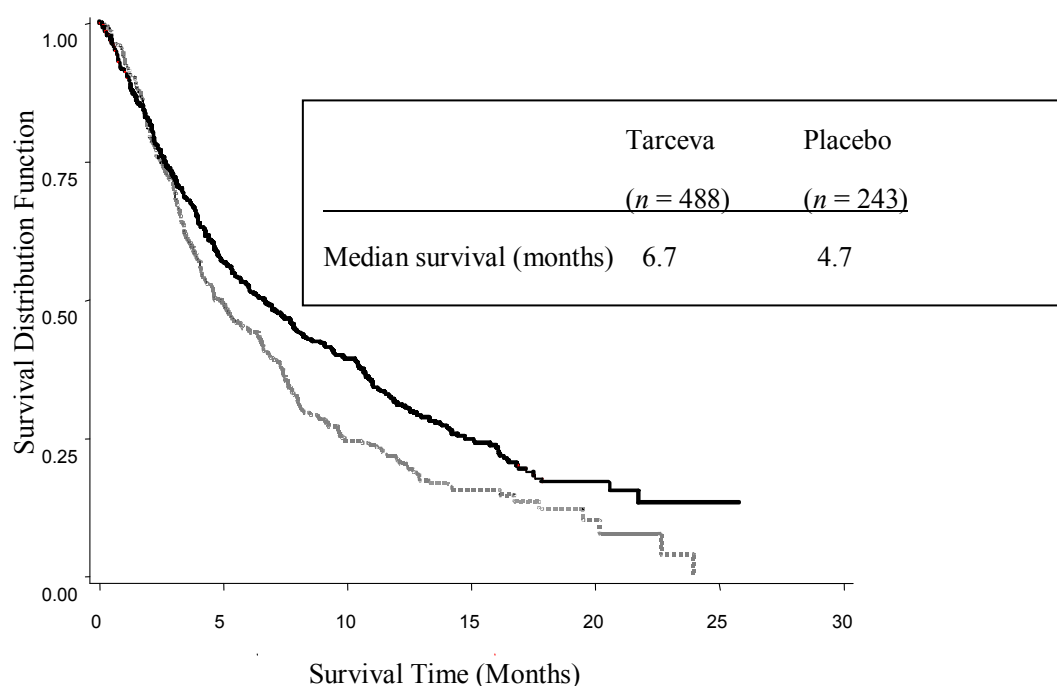
Survival was evaluated in the intent-to-treat population. The median overall survival improved by 42.5% and was 6.7 months in the TARCEVA group compared with 4.7 months in the placebo group (see Figure 3). The primary survival analysis was adjusted for the stratification factors as reported at the time of randomisation (ECOG PS, best response to prior therapy, number of prior



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regimens and exposure to prior platinum) and HER1/EGFR status. In this primary analysis, the adjusted HR for death in the TARCEVA group relative to the placebo group was 0.73 (95% CI: 0.60 – 0.87;  $p = 0.001$ ). The percent of patients alive at 12 months was 31.2% and 21.5%, for the TARCEVA and placebo groups respectively.

**Figure 3: Kaplan-Meier Curve for Overall Survival of Patients by Treatment Group in Study BR.21**



The robustness of the overall survival result was examined in exploratory univariate analyses of a number of patient subsets formed according to stratification factors. The survival benefit with TARCEVA treatment was seen across patient subsets including prior exposure to taxanes, smoking history, gender, age, histology, prior weight loss, time between initial diagnosis and randomisation and geographic location. The HR in the TARCEVA group relative to the placebo group were less than 1.0, suggesting that the survival benefit from TARCEVA was robust across subsets. Of note, the survival benefit of TARCEVA was comparable in patients with a baseline ECOG PS of 2 – 3 (HR = 0.77) or a PS of 0 – 1 (HR = 0.73) and patients who had received one chemotherapy regimen (HR = 0.76) or two or more regimens (HR = 0.76).

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

Summarised in Table 5 are the results for study BR.21, including survival, time to deterioration of lung cancer-related symptoms and progression-free survival.

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**Table 5: Study BR.21 - Efficacy Results**

	<b>TARCEVA</b> <i>n</i> = 488	<b>Placebo</b> <i>n</i> = 243	<i>p</i> -value
<b>Median survival</b>	6.7 months	4.7 months	
<b>Difference between survival curves</b>			0.001
<b>Hazard Ratio<sup>a</sup>, mortality (erlotinib: placebo)</b>	0.73		0.001
<b>95% CI</b>	0.60 - 0.87		
<b>Median time to deterioration in cough<sup>c</sup></b>	6.4 months	3.6 months	0.041
<b>Median time to deterioration in dyspnoea<sup>c</sup></b>	4.6 months	2.8 months	0.031 <sup>b</sup>
<b>Median time to deterioration in pain<sup>c</sup></b>	2.8 months	1.8 months	0.040 <sup>b</sup>
<b>Median progression-free survival</b>	2.2 months	1.8 months	<0.001

<sup>a</sup> adjusted for stratification factors and HER1/EGFR status; a value less than 1.00 favours TARCEVA (primary analysis)

<sup>b</sup> *p*-value adjusted for multiple testing

<sup>c</sup> from the EORTC QLQ-C30 and QLQ-LC13 quality of life questionnaires

Symptom deterioration was measured using the EORTC QLQ-C30 and QLQ-LC13 quality of life questionnaires. Baseline scores of cough, dyspnoea and pain were similar in the two treatment groups. TARCEVA resulted in symptom benefits by significantly prolonging time to deterioration in cough (HR = 0.75), dyspnoea (HR = 0.72) and pain (HR = 0.77) versus placebo. These symptom benefits were not due to an increased use of palliative radiotherapy or concomitant medications in the TARCEVA group.

The median PFS was 2.2 months in the TARCEVA group compared with 1.8 months in the placebo group. The HR for progression, adjusted for stratification factors and HER1/EGFR status, was 0.61 (95% CI: 0.51 – 0.73; *p* < 0.001). The percent of PFS at 6 months was 24.5% and 9.3% respectively, for the TARCEVA and placebo groups.

The objective response rate by RECIST in the TARCEVA group was 8.9% (95% CI: 6.4 – 12.0). The median duration of response was 7.8 months, ranging from 2.2 months – 13.2+ months. Two responses (0.9%, 95% CI: 0.1 – 3.4) were reported in the placebo group. The proportion of patients who experienced complete response, partial response or stable disease was 44.0% and 27.5% respectively, for the TARCEVA and placebo groups (*p* = 0.004).

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### **Pancreatic Cancer – TARCEVA in Combination with Gemcitabine**

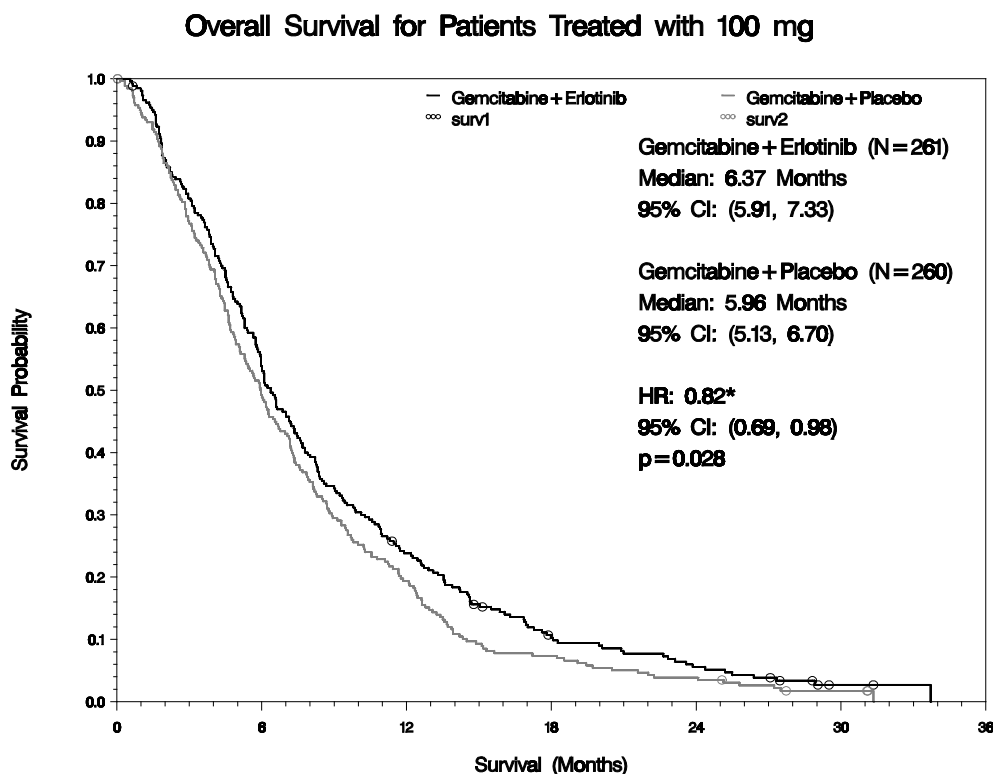
The efficacy and safety of TARCEVA in combination with gemcitabine as a first line treatment was assessed in a randomised, double blind, placebo-controlled trial in 569 patients with locally advanced, unresectable or metastatic pancreatic cancer (Study PA.3). Patients were randomised 1:1 to receive TARCEVA (100 mg or 150 mg) or placebo once daily on a continuous schedule plus gemcitabine IV (1000 mg/m<sup>2</sup>, 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 (approved dose and schedule for pancreatic cancer according to gemcitabine product information). TARCEVA or placebo was taken orally once daily until disease progression or unacceptable toxicity. Study end points included overall survival, response rate and progression-free survival (PFS). Duration of response was also examined. The primary endpoint was survival. A total of 285 patients were randomised to receive gemcitabine plus TARCEVA (261 patients in the 100 mg cohort and 24 patients in the 150 mg cohort) and 284 patients were randomised to receive gemcitabine plus placebo (260 patients in the 100 mg cohort and 24 patients in the 150 mg cohort). Too few observations were made for the 150 mg cohort to draw conclusions.

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 100 mg TARCEVA plus gemcitabine arm (51%) compared with the placebo plus gemcitabine arm (44%). The median time from initial diagnosis to randomisation was approximately 1.0 month. Approximately half of the patients had a baseline ECOG performance status (PS) of 1 and 17% had a baseline ECOG PS of 2. Most patients presented with metastatic disease at study entry as the initial manifestation of pancreatic cancer (77% in the TARCEVA arm, 76% in the placebo arm).

Survival was evaluated in the intent-to-treat population based on follow-up survival data including 551 deaths. Results are presented for the 100 mg dose cohort (504 deaths) in Figure 4. The adjusted HR for death in the TARCEVA group relative to the placebo group was 0.82 (95% CI: 0.69 – 0.98;  $p = 0.028$ ). The percentage of patients alive at 12 months was 23.8% in the TARCEVA group compared to 19.4% in the placebo group. The median overall survival was 6.4 months in the TARCEVA group compared with 6 months in the placebo group.

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**Figure 4: Kaplan-Meier curve for overall survival of patients in TARCEVA 100mg dose cohort by treatment group in Study PA.3**



**Table 6: Study PA.3 Efficacy Results**

	<b>TARCEVA 100 mg plus gemcitabine (n = 261)</b>	<b>Placebo plus gemcitabine (n = 260)</b>	<b>p-value</b>
<b>Median survival</b>	6.4 months	6 months	
<b>Hazard ratio, mortality (TARCEVA:placebo) (95% CI)</b>	0.82 (0.69 – 0.98)		0.028
<b>% patients alive at 12 months</b>	23.8	19.4	

The median PFS was 3.81 months (16.5 weeks) in the TARCEVA group (95% CI; 3.58 – 4.93) compared with 3.55 months (15.2 weeks) in the placebo group (95% CI; 3.29 – 3.75;  $p = 0.006$ ).

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The median duration of response was 5.5 months, ranging from 0.85 months – 12.8+ months. The objective response rate (complete response and partial response) was 8.6% in the TARCEVA group and 7.9% in the placebo group. The proportion of patients who experienced complete response, partial response or stable disease was 59% and 49.4% respectively, for the TARCEVA and placebo groups ( $p = 0.036$ ).

## INDICATIONS

### Non-small cell lung cancer:

TARCEVA is indicated for the first-line treatment of patients with advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) with activating EGFR mutations.

TARCEVA is indicated for maintenance therapy in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not progressed on first-line chemotherapy. Efficacy is influenced by tumour characteristics (see CLINICAL TRIALS).

TARCEVA is also indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.

### Pancreatic cancer:

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

## CONTRAINDICATIONS

TARCEVA is contraindicated in patients with severe hypersensitivity to TARCEVA or to any of the excipients.

## PRECAUTIONS

### EGFR Mutation Status

It is recommended that EGFR mutation testing should be performed prior to initiation of TARCEVA therapy in chemo-naïve patients with advanced or metastatic NSCLC. A well-validated and robust test for activating EGFR mutations should be used.

### Combination with Chemotherapy

Randomised controlled trials have demonstrated that TARCEVA combined with doublet, platinum-based cytotoxic chemotherapy in advanced NSCLC provides no added benefit over cytotoxic chemotherapy alone.

### Interstitial Lung Disease (ILD)

Cases of ILD-like events, including fatalities, have been reported uncommonly in patients receiving TARCEVA for treatment of NSCLC, pancreatic cancer or other advanced solid tumours. In the pivotal Phase III study BR.21 in NSCLC, the incidence of serious ILD-like

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events (0.8%) was the same in both the placebo and TARCEVA groups. In the pancreatic cancer study in combination with gemcitabine, the incidence of ILD-like events was 2.5% in the TARCEVA plus gemcitabine group versus 0.4% in the placebo plus gemcitabine-treated group. The overall incidence in TARCEVA-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.6%. Some examples of 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, lung infiltration and alveolitis. These ILD-like events started from a few days to several months after initiating TARCEVA therapy. Most of the cases were associated with confounding or contributing factors such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease or pulmonary infections. A causal association of ILD-like events to TARCEVA therapy has not been established.

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

### **ECG Effects**

*In vitro* studies indicate that TARCEVA blocks the hERG K<sup>+</sup> channel, producing 20% inhibition at concentrations 1.6 – 8 times higher than the peak free TARCEVA concentration in humans and therefore has the potential to inhibit cardiac action potential repolarisation. The clinical significance of these findings is unknown and adverse ECG effects have not been observed in human studies to date.

### **Diarrhoea and Dehydration**

Diarrhoea has occurred in patients on TARCEVA and moderate or severe diarrhoea should be treated with loperamide. In some cases, dose reduction may be necessary. In the event of severe or persistent diarrhoea, nausea, anorexia or vomiting associated with dehydration, TARCEVA therapy should be interrupted and appropriate measures should be taken to treat the dehydration.

### **Hypokalaemia, Renal Failure**

There have been rare reports of hypokalaemia and renal failure (including fatalities). Some reports of renal failure were secondary to severe dehydration due to diarrhoea, vomiting and/or anorexia, while others were confounded by concomitant chemotherapy. In more severe or persistent cases of diarrhoea, or cases leading to dehydration, particularly in groups of patients with aggravating risk factors (concomitant medications, symptoms or diseases or other predisposing conditions including advanced age), TARCEVA therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patients intravenously. In addition, renal function and serum electrolytes including potassium should be monitored in patients at risk of dehydration.

### **Lactose Intolerance**

TARCEVA tablets contain lactose and should not be administered to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

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### **Hepatotoxicity, Hepatitis, Hepatic Failure**

Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin) have been observed infrequently. These were mainly mild or moderate in severity, transient in nature or associated with liver metastases.

Rare cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported during use of TARCEVA. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medications. Therefore, in such patients, periodic liver function testing should be considered.

TARCEVA treatment should be interrupted or discontinued if changes in liver function are severe (see PRECAUTIONS; Hepatic Impairment and DOSAGE AND ADMINISTRATION; Special Dosage Instructions, Hepatic Impairment).

### **Gastrointestinal Perforations**

Patients receiving TARCEVA are at an increased risk of developing gastrointestinal perforation, which was observed uncommonly (including some cases with a fatal outcome). 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. TARCEVA should be permanently discontinued in patients who develop gastrointestinal perforation (see ADVERSE EFFECTS).

### **Bullous and Exfoliative Skin Disorders**

Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal (see ADVERSE EFFECTS). TARCEVA treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliative conditions.

### **Ocular Disorders**

Very rare cases of 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 which are also risk factors for corneal perforation/ulceration. TARCEVA therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain (see ADVERSE EFFECTS).

### **Genotoxicity**

TARCEVA 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 micronucleus test. Under the conditions of these assays, TACEVA did not cause genetic damage.

### **Carcinogenesis**

TARCEVA has not been tested for carcinogenic potential.



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### **Effects on Fertility**

TARCEVA did not impair fertility in male rats given doses that result in plasma drug concentrations similar to that of humans. TARCEVA administered at 10 mg/kg/day (1.5 times the clinical dose based on relative AUC) for 2 weeks prior to mating until day 7 of gestation affected ovulation in female rats, resulting in a reduction in the number of corpora lutea.

### **Use in Pregnancy – Category C**

There are no adequate or well-controlled studies in pregnant women using TARCEVA.

When TARCEVA was administered during organogenesis, reduced foetal/birth weight and increases in the incidence of small, incompletely inflated lung lobes and incomplete or absent ossification were observed in rats at doses that resulted in plasma concentrations comparable to those in humans. In rabbits, foetal weight was reduced at plasma concentrations 1.5 times those of humans and the incidence of absent ossification was increased at doses producing 4.5 times the clinical exposure. Embryo/foetal lethality and/or abortion was seen in rats and rabbits given doses that result in plasma drug concentrations 4.5 – 6.5 times those of humans. Embryo/foetal toxicity was associated with maternal toxicity.

Women of childbearing potential must be advised to avoid pregnancy while on TARCEVA. Adequate contraceptive methods should be used during therapy and for at least 2 weeks after completing therapy. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the foetus.

### **Use in Lactation**

It is not known whether TARCEVA is excreted in human milk. Because of the potential harm to the infant, mothers should be advised against breastfeeding while receiving TARCEVA.

### **Paediatric Use**

The safety and efficacy of TARCEVA has not been studied in patients under the age of 18 years.

### **Use in the Elderly**

Of the total number of patients participating in the Phase III study BR. 21, 62% were less than 65 years of age and 38% of patients were aged 65 years or older. The survival benefit was maintained across both age groups (see CLINICAL TRIALS). No meaningful differences in safety or pharmacokinetics were observed between younger and older patients. Therefore, no dosage adjustments are recommended in elderly patients.

### **Renal Impairment**

The safety and efficacy of TARCEVA has not been studied in patients with renal impairment.

### **Hepatic Impairment**

In view of the variability in pharmacokinetics, TARCEVA should be used with caution in patients with hepatic impairment and the dose tailored to individual patients (see Pharmacokinetics in Special Populations, Hepatic Impairment).

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Patients with hepatic impairment are at increased risk of hepatic failure during treatment with TARCEVA. Therefore, close monitoring of hepatic function is recommended. TARCEVA treatment should be interrupted or discontinued if changes in hepatic function are severe (see PRECAUTIONS; Hepatotoxicity, Hepatitis, Hepatic Failure and DOSAGE AND ADMINISTRATION; Special Dosage Instructions, Hepatic Impairment).

The safety and efficacy of TARCEVA have not been studied in patients with severe hepatic impairment (total serum bilirubin > 3 x ULN). Use of TARCEVA in patients with severe hepatic impairment is not recommended.

### **Ability to Drive or Operate Machinery**

No studies on the effects on the ability to drive and use machines have been performed, however, TARCEVA is not associated with impairment of mental ability.

## **INTERACTIONS WITH OTHER MEDICINES**

TARCEVA is metabolised by the hepatic cytochromes in humans, primarily CYP3A4/CYP3A5 and to a lesser extent by CYP1A2 and the pulmonary isoform CYP1A1. Potential interactions may occur with medicines that are metabolised by, or are inhibitors or inducers of, these enzymes.

Potent inhibitors of CYP3A4 activity decrease erlotinib metabolism and increase erlotinib plasma concentrations. Inhibition of CYP3A4 metabolism by ketoconazole (200 mg orally twice daily for 5 days) resulted in increased exposure to TARCEVA (86% in median TARCEVA AUC) and a 69% increase in maximum concentration ( $C_{max}$ ) when compared to TARCEVA alone. When TARCEVA was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2, TARCEVA exposure [AUC] and  $C_{max}$  increased by 39% and 17% respectively. Therefore, caution should be used when administering TARCEVA with potent CYP3A4 or combined CYP3A4/CYP1A2 inhibitors such as ketoconazole, atazanavir, clarithromycin, erythromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin and voriconazole. In these situations, the dose of TARCEVA should be reduced if toxicity is observed.

Potent inducers of CYP3A4 increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations. Induction of CYP3A4 metabolism by rifampicin (600 mg orally, 4 times a day for 7 days) resulted in a 69% decrease in the median TARCEVA AUC, following a 150 mg dose of TARCEVA, as compared to TARCEVA alone.

In another study, pre-treatment and co-administration of rifampicin with a single 450 mg dose of TARCEVA resulted in a decreased mean erlotinib exposure [AUC], which was 57.5% of a single 150 mg TARCEVA dose in the absence of rifampicin treatment. Therefore, caution should be used when administering TARCEVA with potent CYP3A4 inducers such as rifampicin, rifabutin, rifapentin, phenytoin, carbamazepine, phenobarbital and St. John's Wort. Alternative treatments lacking potent CYP3A4 inducing activity should be considered when possible. For patients who require concomitant treatment with TARCEVA and a potent CYP3A4 inducer such as rifampicin, an increase in dose to 300 mg should be considered while their safety is closely monitored and if well tolerated for more than 2 weeks, a further increase to 450 mg could be considered with close safety monitoring. Higher doses have not been studied in this setting.

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Pre-treatment or co-administration of TARCEVA did not alter the clearance of the prototypical CYP3A4 substrates midazolam and erythromycin. Significant interactions with the clearance of other CYP3A4 substrates are therefore unlikely. Oral availability of midazolam did appear to decrease by up to 24%, which was however not attributed to effects on CYP3A4 activity.

The solubility of TARCEVA is pH dependent. TARCEVA solubility decreases as pH increases. Medicines that alter the pH of the upper gastrointestinal tract may alter the solubility of TARCEVA and hence its bioavailability. Co-administration of TARCEVA with omeprazole, a proton pump inhibitor, decreased the TARCEVA exposure [AUC] and  $C_{max}$  by 46% and 61% respectively. There was no change to  $T_{max}$  or half-life. Concomitant administration of TARCEVA with 300 mg ranitidine, a  $H_2$ -receptor antagonist, decreased TARCEVA exposure [AUC] and  $C_{max}$  by 33% and 54% respectively. Therefore, co-administration of TARCEVA with medicines that reduce gastric acid production should be avoided where possible. Increasing the dose of TARCEVA is not likely to compensate for loss of exposure. However, when TARCEVA was dosed in a staggered manner 2 hours before or 10 hours after ranitidine 150 mg twice daily, TARCEVA exposure [AUC] and  $C_{max}$  decreased by 15% and 17% respectively. If patients need to be treated with such medicines, an  $H_2$ -receptor antagonist such as ranitidine should be considered and used in a staggered manner. TARCEVA must be taken at least 2 hours before or 10 hours after the  $H_2$ -receptor antagonist dosing.

International Normalized Ratio (INR) elevations and bleeding events, including gastrointestinal bleeding, have been reported in clinical studies, some associated with concomitant warfarin administration. Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.

The combination of TARCEVA and a statin may increase the potential for statin-induced myopathy, including rhabdomyolysis, which was observed rarely.

In a Phase Ib study, there were no significant effects of gemcitabine on the pharmacokinetics of TARCEVA nor were there significant effects of TARCEVA on the pharmacokinetics of gemcitabine.

The impact of smoking on TARCEVA efficacy is not known, however, smokers should be advised to stop smoking as cigarette smoking, which is known to induce CYP1A1 and CYP1A2, has been shown to reduce TARCEVA exposure by 50 – 60% (see PHARMACOLOGY; Pharmacokinetics in Special Populations).

## ADVERSE EFFECTS

Safety evaluation of TARCEVA is based on the data from more than 1200 patients treated with at least one 150 mg dose of TARCEVA monotherapy, and more than 300 patients who received TARCEVA 100 mg or 150 mg in combination with gemcitabine.

The incidence of adverse reactions reported with TARCEVA alone or in combination with chemotherapy are summarised in the tables below and are based on data from clinical trials. The listed adverse reactions were those reported in at least 10% (in the TARCEVA group) of patients and occurred more frequently ( $\geq 3\%$ ) in patients treated with TARCEVA than in the comparator arm.

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### **TARCEVA Monotherapy**

The adverse reactions listed in Table 7 are based on data from the pivotal study BR.21 conducted in 731 patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Patients were randomised 2:1 to receive TARCEVA 150 mg or placebo, taken orally once daily until disease progression or unacceptable toxicity.

The most frequent adverse reactions were rash and diarrhoea (any Grade, 75% and 54% respectively), most were Grade 1 – 2 in severity and manageable without intervention. Grade 3 or Grade 4 rash and diarrhoea occurred in 9% and 6% respectively in TARCEVA-treated patients and each resulted in study discontinuation in 1% of patients. Rash and diarrhoea diminished following discontinuation of TARCEVA. Dose reduction for rash and diarrhoea was needed in 6% and 1% of patients respectively. In study BR.21, the median time to onset of rash was 8 days and the median time to onset of diarrhoea was 12 days.

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**Table 7: Adverse reactions occurring more frequently ( $\geq 3\%$ ) in TARCEVA-treated group than in the placebo group and in  $\geq 10\%$  of patients in the TARCEVA group in study BR.21**

	TARCEVA <i>n</i> = 485			Placebo <i>n</i> = 242		
NCI-CTC Grade	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
Total patients with any AE	99	40	22	96	36	22
<i>Skin and subcutaneous tissue disorders</i>						
Rash	75	8	<1	17	0	0
Pruritus	13	<1	0	5	0	0
Dry skin	12	0	0	4	0	0
<i>Gastrointestinal disorders</i>						
Diarrhoea	54	6	<1	18	<1	0
Nausea	33	3	0	24	2	0
Vomiting	23	2	<1	19	2	0
Stomatitis	17	<1	0	3	0	0
Abdominal pain	11	2	<1	7	1	<1
<i>General disorders and administration site conditions</i>						
Fatigue	52	14	4	45	16	4
<i>Metabolism and nutrition disorders</i>						
Anorexia	52	8	1	38	5	<1
<i>Respiratory, thoracic and mediastinal disorders</i>						
Dyspnoea	41	17	11	35	15	11
Cough	33	4	0	29	2	0
<i>Infections and infestations*</i>						
Infection	24	4	0	15	2	0
<i>Eye disorders</i>						
Conjunctivitis	12	<1	0	2	<1	0
Keratoconjunctivitis sicca	12	0	0	3	0	0

\* severe infections, with or without neutropenia, have included pneumonia, sepsis and cellulitis.

In another double-blind, randomised, placebo-controlled Phase III study (BO18192) conducted in 889 patients with advanced, recurrent or metastatic NSCLC following first-line standard platinum-based chemotherapy, no new safety signals were identified.

The most frequent adverse reaction seen in patients treated with TARCEVA in study BO18192 were rash and diarrhoea (any Grade, 49% and 20%, respectively), most were Grade 1 – 2 in

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severity and manageable without intervention. Grade 3 rash and diarrhoea occurred in 6% and 2% of patients, respectively. No Grade 4 rash or diarrhoea was observed. Rash and diarrhoea resulted in discontinuation of TARCEVA in 1% and < 1% of patients respectively. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in 8.3% and 3% of patients, respectively.

In the open-label, randomised phase III study ML 20650, conducted in 154 patients, the safety of TARCEVA for first-line treatment of NSCLC patients with EGFR activating mutations was assessed in 75 patients; no new safety signals were observed in these patients.

The most frequent adverse reactions seen in patients treated with TARCEVA in study ML 20650 were rash and diarrhoea (any Grade 80% and 57%, respectively), most were Grade 1 - 2 in severity and manageable without intervention. Grade 3 rash and diarrhoea occurred in 9% and 4% of patients, respectively. No Grade 4 rash or diarrhoea was observed. Both rash and diarrhoea resulted in discontinuation of TARCEVA in 1% of patients. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in 11% and 7% of patients, respectively.

### **TARCEVA in Combination with Chemotherapy**

The adverse reactions listed in Table 8 are based on the TARCEVA arm data from a controlled clinical trial (PA.3) where 259 patients with pancreatic cancer received TARCEVA 100 mg plus gemcitabine compared to 256 patients in the placebo plus gemcitabine arm.

The most frequent adverse reactions in study PA.3 in pancreatic cancer patients receiving TARCEVA 100 mg plus gemcitabine were fatigue (73%), rash (69%) and diarrhoea (48%). In the TARCEVA plus gemcitabine arm, Grade 3 or Grade 4 rash and diarrhoea were reported in 5% of patients. The median time to onset of rash and diarrhoea was 10 days and 15 days respectively. Rash and diarrhoea 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 TARCEVA 150 mg plus gemcitabine cohort (23 patients) was associated with a higher rate of certain class-specific adverse reactions including rash and required more frequent dose reduction or interruption.

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**Table 8: Adverse reactions occurring  $\geq 10\%$  and more frequently ( $\geq 3\%$ ) in TARCEVA 100 mg plus gemcitabine-treated patients than in the placebo plus gemcitabine group in Study PA.3**

	TARCEVA plus gemcitabine <i>n</i> = 259			Placebo plus gemcitabine <i>n</i> = 256		
NCI-CTC Grade	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
Total patients with any AE	99	48	22	97	48	16
<i>Skin and subcutaneous tissue disorders</i>						
Rash	69	5	0	30	1	0
Alopecia	14	0	0	11	0	0
<i>Gastrointestinal disorders</i>						
Diarrhoea	48	5	<1	36	2	0
Stomatitis	22	<1	0	12	0	0
Dyspepsia	17	<1	0	13	<1	0
Flatulence	13	0	0	9	<1	0
<i>Metabolism and nutrition disorders</i>						
Weight decreased	39	2	0	29	<1	0
<i>General disorders and administration site conditions</i>						
Pyrexia	36	3	0	30	4	0
Fatigue	73	14	2	70	13	2
Rigors	12	0	0	9	0	0
<i>Infections and infestations</i>						
Infection*	31	3	<1	24	6	<1
<i>Psychiatric disorders</i>						
Depression	19	2	0	14	<1	0
<i>Respiratory, thoracic and mediastinal disorders</i>						
Cough	16	0	0	11	0	0
<i>Nervous system disorders</i>						
Headache	15	<1	0	10	0	0
Neuropathy	13	1	<1	10	<1	0

\*severe infections, with or without neutropenia, have included pneumonia, sepsis and cellulitis.



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### **Further Information on Adverse Reactions of Special Interest:**

The following adverse reactions have been observed in patients who received TARCEVA monotherapy or TARCEVA 100 mg and 150 mg in combination with gemcitabine.

The following terms are used to rank the adverse reactions by frequency: very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ); very rare ( $< 1/10,000$ ) including isolated reports.

Very common adverse reactions are presented in Tables 7 and 8, adverse events in other frequency categories are summarised below:

#### **Gastrointestinal disorders:**

Gastrointestinal perforations have been reported uncommonly (in less than 1% of patients) with TARCEVA treatment, in some cases with a fatal outcome (see PRECAUTIONS). Cases of gastrointestinal bleeding have been reported commonly (including some fatalities), some associated with concomitant warfarin administration (see PRECAUTIONS; Interactions with Other Medicines) and some with concomitant NSAID administration.

#### ***Hepatobiliary disorders:***

Liver function test abnormalities (including elevated alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin) have been observed commonly in clinical trials of TARCEVA. In study PA.3, these occurred very commonly. They were mainly mild or moderate in severity, transient in nature or associated with liver metastases. Rare cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported during use of TARCEVA. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medications. (see PRECAUTIONS; Hepatotoxicity, Hepatitis, Hepatic Failure).

#### **Eye disorders:**

Corneal ulcerations or perforations have been reported very rarely in patients receiving TARCEVA treatment (see PRECAUTIONS).

Keratitis and conjunctivitis has been reported commonly with TARCEVA. Abnormal eyelash growth including: in-growing eyelashes, excessive growth and thickening of the eyelashes have been reported (see PRECAUTIONS).

#### **Respiratory, thoracic and mediastinal disorders:**

There have been uncommon reports of serious interstitial lung disease, including fatalities, in patients receiving TARCEVA for treatment of NSCLC and other advanced solid tumours.

Cases of epistaxis have also been reported commonly in both the NSCLC and the pancreatic cancer trials.

#### ***Skin and subcutaneous tissue disorders:***

Rash has been reported very commonly in patients receiving TARCEVA and in general, manifests as a mild or moderate erythematous and papulopustular rash, which may occur or worsen in sun exposed areas. For patients who are exposed to sun, protective clothing and/or use of sunscreen may be advisable. Acne, dermatitis acneiform and folliculitis have been observed

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commonly, most of these events were mild or moderate and non-serious. Skin fissures, mostly non-serious, were reported commonly and in the majority of cases were associated with rash and dry skin. Other mild skin reactions such as hyperpigmentation have been observed uncommonly (in less than 1% of patients).

Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal (see PRECAUTIONS). Hair and nail changes, mostly non-serious, were reported in clinical trials, e.g. paronychia was reported commonly and hirsutism, eyelash/eyebrow changes and brittle and loose nails were reported uncommonly.

### ***Cardiovascular disorders:***

In the pivotal pancreatic cancer trial there was an excess of myocardial infarction/ischaemia (2.3% vs 1.2%) and cerebrovascular accidents (2.3% vs 0%) in the TARCEVA/gemcitabine group compared to the placebo/gemcitabine group.

### **Post-Marketing Experience**

### ***Skin and subcutaneous tissue disorders:***

Hair and nail changes, mostly non-serious, have been reported uncommonly from post-marketing surveillance, e.g. hirsutism, eyelash/eyebrow changes, paronychia and brittle and loose nails.

## **DOSAGE AND ADMINISTRATION**

### **Non-Small Cell Lung Cancer**

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

When dose adjustment is necessary, reduce in 50 mg steps.

### **Pancreatic cancer**

The recommended daily dose of TARCEVA is 100 mg taken at least one hour before or two hours after the ingestion of food, in combination with gemcitabine (see the gemcitabine Product Information for the correct dosage of gemcitabine in pancreatic cancer). Treatment should be continued until disease progression or unacceptable toxicity occurs.

### **Special Dosage Instructions**

Concomitant use of CYP3A4 substrates and modulators may require dose adjustment (see PRECAUTIONS; Interactions with Other Medicines).

### ***Hepatic impairment***

TARCEVA treatment should be interrupted or discontinued if;

- there is a doubling of total serum bilirubin and/or tripling of serum transaminases in patients with baseline hepatic impairment

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- total serum bilirubin is  $> 3 \times$  ULN and/or serum transaminases are  $> 5 \times$  ULN in patients with normal pre-treatment values. (See PRECAUTIONS; Hepatic Impairment)

## OVERDOSAGE

Single oral doses of TARCEVA up to 1000 mg in healthy subjects and up to 1600 mg given as a single dose once weekly in cancer patients have been tolerated. Repeated twice daily doses of 200 mg in healthy subjects were poorly tolerated after only a few days of dosing. Based on the data from these studies, severe adverse events such as diarrhoea, rash and possibly liver transaminase elevation may occur above the recommended dose of 150 mg. In case of suspected overdose, TARCEVA should be withheld and symptomatic treatment initiated. Treatment should consist of general supportive measures.

Contact the Poisons Information Centre for advice on management of overdose.

## PRESENTATION AND STORAGE CONDITIONS

TARCEVA 25 mg, 100 mg and 150 mg film-coated tablets are available in blisters containing 30 tablets.

TARCEVA 25 mg film-coated tablets are white to yellowish, round, biconvex tablets marked with 'TARCEVA 25' and logo in brownish yellow on one side.

TARCEVA 100 mg film-coated tablets are white to yellowish, round, biconvex tablets marked with 'TARCEVA 100' and logo in grey on one side.

TARCEVA 150 mg film-coated tablets are white to yellowish, round, biconvex tablets marked with 'TARCEVA 150' and logo in brown on one side.

Store below 30°C.

## Disposal of Medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via waste water and disposal through household waste should be avoided. Unused or expired medicines should be returned to a pharmacy for disposal.

## NAME AND ADDRESS OF THE SPONSOR

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Dee Why NSW 2099  
AUSTRALIA

Customer enquiries: 1800 233 950

**Attachment 1: Product information for AusPAR Tarceva Erlotinib Roche Products Pty Ltd PM-2011-01993-3-4 Final 7 January 2013. This Product Information was approved at the time this AusPAR was published.**

## **POISON SCHEDULE**

Schedule 4 – Prescription only medicine.

## **DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)**

30 January 2006

## **DATE OF MOST RECENT AMENDMENT**

29 June 2012