In maintenance therapy and relapsed or refractory NSCLC

Extending survival *for moments that matter*

Safety and effectiveness have not been studied in pediatric patients.

Tarceva is approved in NSCLC for a broad* patient population, irrespective of histology or biomarker status

*Tarceva trials included a broad intent-to-treat population; please see pages 7 and 13 for study designs.

Non-small cell lung cancer (NSCLC) indications

Tarceva monotherapy is indicated for:

- the 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.
- the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.

Results from two, multicenter, placebo-controlled, randomized, phase III 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.

Please see important safety information throughout this piece, on pages 22-23, and in enclosed full prescribing information.

Tarceva® erlotinib tablets

Proven to prolong survival

In maintenance therapy and relapsed or refractory NSCLC

Tarceva is proven to extend overall survival[1]

As maintenance therapy in stage IIIB/IV NSCLC

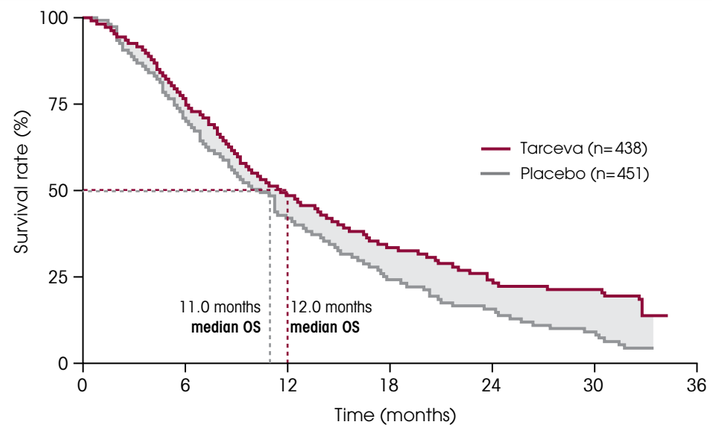
Tarceva is approved as maintenance therapy for a broad patient population[1]

- NCCN guidelines recommend erlotinib as an option for maintenance therapy based on the SATURN trial.[2]

Tarceva significantly prolonged overall survival in a broad patient population[1]

19% reduction in risk of death[1]

OS in the SATURN ITT* population



Hazard ratio=0.81
(95% CI=0.70-0.95)
Log-rank *P*=0.0088

Tarceva significantly prolonged progression-free survival in a broad patient population, based on investigator's assessment[1]

- Tarceva reduced risk of cancer progression or death in the ITT population of the SATURN trial by 29% (HR=0.71; 95% CI=0.62-0.82; *P*<0.0001; median: 2.8 months with Tarceva vs 2.6 months with placebo).[1]

In both NSCLC treatment settings, serious adverse reactions have occurred with Tarceva; the most common adverse reactions associated with Tarceva are generally manageable[1]

- Warnings and precautions associated with Tarceva, including fatalities, in NSCLC include Interstitial Lung Disease (ILD), renal failure, hepatotoxicity, hepatic impairment, gastrointestinal perforation, bullous and exfoliative skin disorders, ocular disorders, and elevated INR and potential bleeding. Tarceva is pregnancy category D.[1]
- The most common adverse reactions in patients with NSCLC receiving Tarceva monotherapy 150 mg as maintenance therapy were grades 1 and 2 rash (43.2%) and diarrhea (18.5%).[1]
- The most common adverse reactions in patients receiving Tarceva monotherapy 150 mg for relapsed or refractory NSCLC were grades 1 and 2 rash (~66%) and diarrhea (~47%).[1]

*Intent to treat.

In relapsed or refractory stage IIIB/IV NSCLC

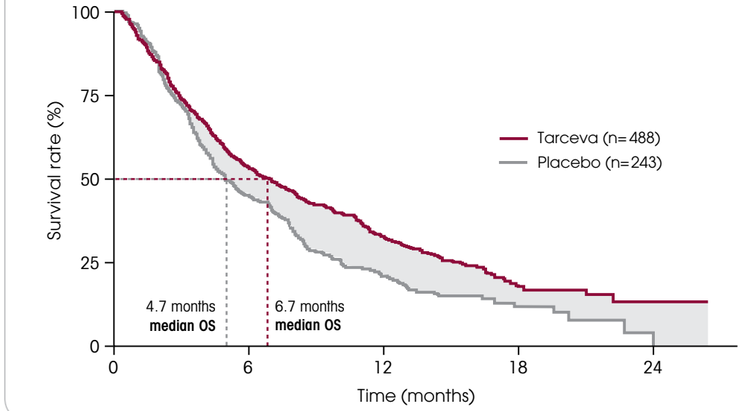
Tarceva is approved in the relapsed or refractory setting for a broad patient population[1]

- NCCN guidelines recommend erlotinib as an option for second-line NSCLC therapy based on the results of the BR.21 trial.[2]

Tarceva significantly prolonged overall survival in a broad patient population[1]

27% reduction in risk of death[1]

OS in the BR.21 ITT* population



Hazard ratio=0.73
(95% CI=0.61-0.86)
Log-rank *P*<0.001

Based on a retrospective exploratory analysis, the overall survival benefit in the ITT population extended to squamous cell carcinoma, a difficult-to-treat disease[3-5]

- Tarceva reduced the risk of death by 33% (HR=0.67; 95% CI=0.5-0.9; *P*=0.007; median: 5.6 months with Tarceva vs 3.6 months with placebo).[3]

Tarceva significantly prolonged progression-free survival in a broad patient population[1]

- Tarceva reduced risk of cancer progression or death in the ITT population of the BR.21 trial by 41% (HR=0.59; 95% CI=0.50-0.70; *P*<0.001; median: 2.3 months with Tarceva vs 1.8 months with placebo).[1]

Tarceva® erlotinib tablets

*Intent to treat.

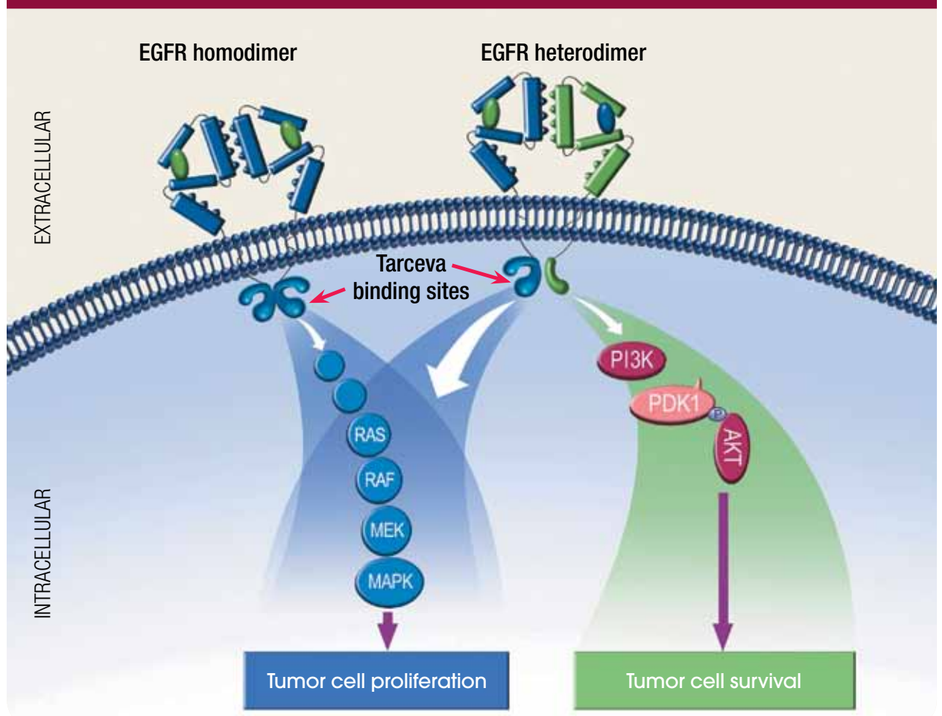
Please see important safety information throughout this piece, on pages 22-23, and in enclosed full prescribing information.

Tarceva in preclinical studies

Limits tumor cell proliferation and tumor cell survival

EGFR is an important signaling receptor in NSCLC[6]

Tarceva is designed to inhibit key signaling pathways within NSCLC tumor cells[7-9]



- Epidermal growth factor receptor (EGFR) is essential for regulation of normal cell growth and differentiation, but its dysregulation can lead to uncontrolled cell proliferation and malignancy.[6]
- Tarceva binds to the EGFR homodimer and heterodimer tyrosine kinase domains. *This activity may inhibit both tumor cell proliferation and tumor cell survival.*[8]
- **The mechanism of clinical antitumor action of Tarceva is not fully characterized.**[1]

Tarceva in the maintenance setting

Tarceva® erlotinib tablets

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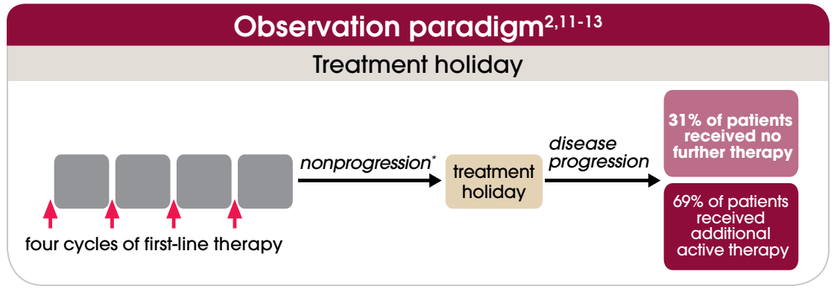
Tarceva as maintenance therapy in stage IIIB/IV NSCLC

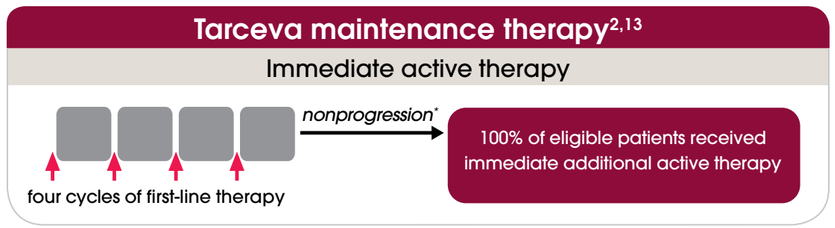
Ensures that patients receive immediate active therapy after first-line treatment, which has been proven to prolong overall survival[1,10]

In several trials studying different maintenance regimens, 31% of patients given a treatment holiday did not receive any further active therapy[11-13]

- Rapid progression, declining performance status, and increased symptom burden may render patients unsuitable to receive further treatment.[12,14]



Immediate maintenance therapy with Tarceva enables more patients to receive active therapy after first-line treatment[10,13]



As maintenance therapy, Tarceva offers:

- An oral formulation that provides an alternative to intravenous infusions.
- A proven survival benefit (HR=0.81; 95% CI=0.70-0.95; *P*=0.0088; median: 12.0 months with Tarceva vs 11.0 months with placebo).[1]

Important safety information

- There have been reports of serious Interstitial Lung Disease (ILD)-like events, including fatalities, in patients receiving Tarceva.[1]

*Complete response/partial response/stable disease.

"[M]aintenance therapy may achieve its effect because active drugs administered before disease progression can prevent complications of the disease from rendering patients unable to receive [further therapy]."[14]

Jong-Mu Sun, MD
Samsung Medical Center
Sungkyunkwan University
Seoul, South Korea

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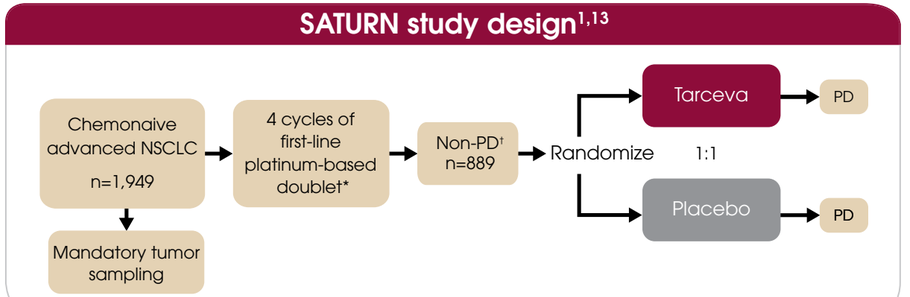
Tarceva as maintenance therapy in stage IIIB/IV NSCLC

Approved after first-line chemotherapy for a broad patient population, irrespective of histology or biomarker status[1]

NCCN guidelines recommend erlotinib as an option for maintenance therapy based on the SATURN trial[2]

- Tarceva is the only FDA-approved oral option for NSCLC maintenance therapy.[1]
- Tarceva monotherapy is indicated for the maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.[1]
- Results from two, multicenter, placebo-controlled, randomized, phase III 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.[1]

SATURN was an international, placebo-controlled, randomized, double-blind phase III study[1,13]



- SATURN included patients with the following histology types[1,13]:
  - Squamous cell carcinoma
  - Nonsquamous cell carcinoma (adenocarcinoma, large-cell, other)
- Coprimary end points[1,13]
  - Progression-free survival (PFS) in all patients
  - PFS in patients with EGFR IHC-positive tumors
- Secondary end points[13]
  - Overall survival (OS) in all patients and those with EGFR IHC-positive tumors
  - OS and PFS in EGFR IHC-negative tumors
  - Safety
- The intent-to-treat population in the SATURN trial included patients of varying age, sex, stage (IIIB or IV), race, ECOG performance status (0 or 1), smoking status, histology, response to prior chemotherapy, EGFR IHC status, and EGFR mutation status.[1,13]

*Cisplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/docetaxel, cisplatin/vinorelbine, carboplatin/gemcitabine, carboplatin/docetaxel, or carboplatin/paclitaxel.[3]
†Progressive disease.

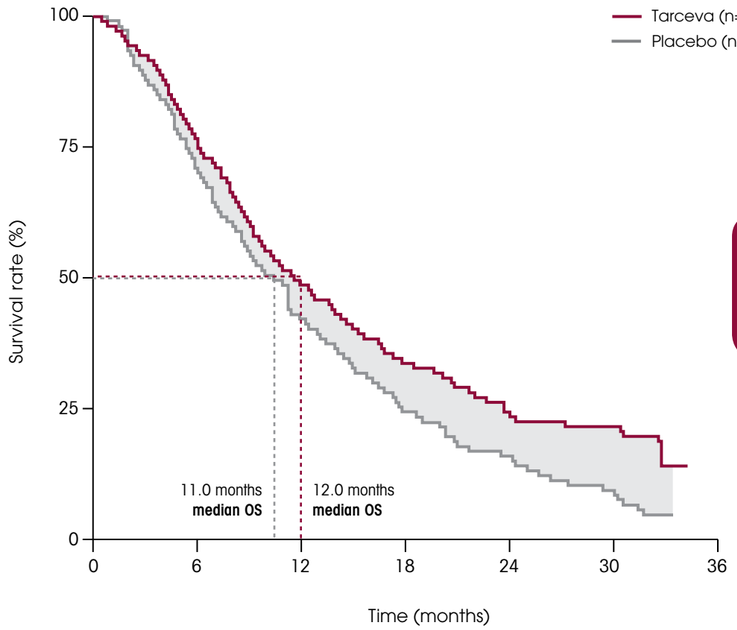
Tarceva® erlotinib tablets

Tarceva as maintenance therapy in stage IIIB/IV NSCLC

Significantly prolonged overall survival in a broad patient population[1]

19% reduction in risk of death[1]

OS in the SATURN ITT* population



Hazard ratio=0.81
(95% CI=0.70-0.95)
Log-rank *P*=0.0088

Important safety information

- Cases, including fatalities, of hepatic failure; hepatorenal syndrome; acute renal failure; gastrointestinal perforation; and bullous, blistering, and exfoliative skin conditions, including cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, have been reported during use of Tarceva.[1]
- Renal insufficiency and corneal perforation/ulceration have also been reported during use of Tarceva.[1]

"[T]he results from the SATURN study provide a strong rationale for introducing Tarceva as a maintenance therapy in this difficult-to-treat disease."[15]

Federico Cappuzzo, MD
Istituto Clinico Humanitas IRCCS
Milan, Italy

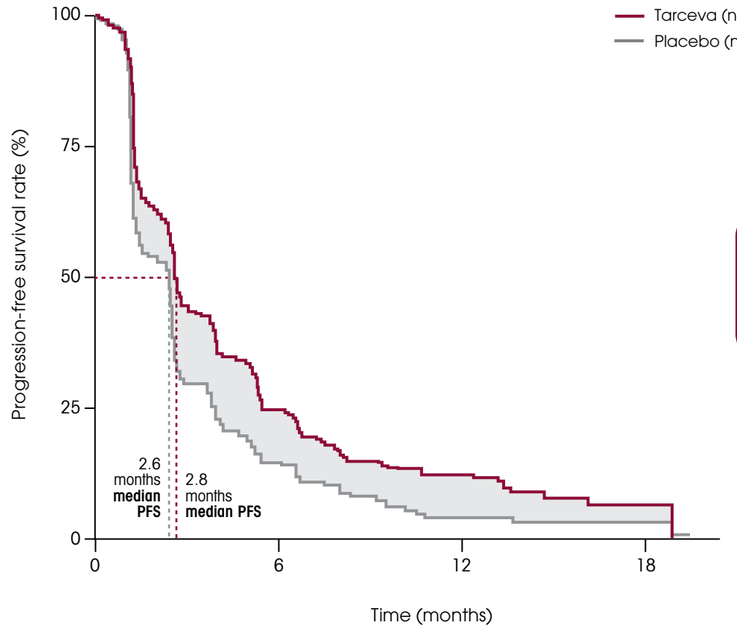
*Intent to treat.

Tarceva as maintenance therapy in stage IIIB/IV NSCLC

Significantly prolonged progression-free survival in a broad patient population[1]

29% reduction in risk of cancer progression or death[1]

PFS based on investigator's assessment in the SATURN ITT* population



Hazard ratio=0.71
(95% CI=0.62-0.82)
Log-rank *P*<0.0001

*Intent to treat.

Tarceva® erlotinib tablets

Please see important safety information throughout this piece, on pages 22-23, and in enclosed full prescribing information.

Adverse reactions with Tarceva as maintenance therapy for advanced NSCLC

Serious adverse reactions have occurred with Tarceva; the most common adverse reactions associated with Tarceva are generally manageable[1]

- Serious adverse reactions have been associated with Tarceva therapy.[1]
  - Warnings and precautions associated with Tarceva, including fatalities, in NSCLC include Interstitial Lung Disease (ILD), renal failure, hepatotoxicity, hepatic impairment, gastrointestinal perforation, bullous and exfoliative skin disorders, ocular disorders, and elevated INR and potential bleeding. Tarceva is pregnancy category D.[1]

Most common treatment-related adverse reactions in the SATURN trial[1]*

Adverse reaction	Tarceva n=433		Placebo n=445	
NCI-CTC grade†	Any grade	Grade 3	Any grade	Grade 3
MedDRA preferred term	%	%	%	%
Rash	49.2	6.0	5.8	0
Diarrhea	20.3	1.8	4.5	0
Anorexia	9.2	<1	4.9	<1
Fatigue	9.0	1.8	5.8	1.1
Pruritus	7.4	<1	2.7	0
Acne	6.2	<1	0	0
Dermatitis acneiform	4.6	<1	1.1	0
Dry skin	4.4	0	<1	0
Weight decreased	3.9	<1	<1	0
Paronychia	3.9	<1	0	0

*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.[1]

† There were no grade 4 reactions in SATURN.[1]

- The most common adverse reactions in patients with NSCLC receiving Tarceva monotherapy 150 mg as maintenance therapy were grades 1 and 2 rash (43.2%) and diarrhea (18.5%).[1]

SATURN trial	Study discontinuation[1]		Dose reduction or interruption[1]	
	Rash %	Diarrhea %	Rash %	Diarrhea %
	1.2	0.5	5.1	2.8

"Currently, the choice of agent depends on a number of factors, including the patient's comorbidities, toxicity from previous treatments, the risk for neutropenia, smoking history, and patient preference."[4]

Thomas Stinchcombe, MD
Lineberger Comprehensive Cancer Center
University of North Carolina at Chapel Hill
Chapel Hill, NC

Safety and effectiveness have not been studied in pediatric patients.

Tarceva® erlotinib tablets

Please see important safety information throughout this piece, on pages 22-23, and in enclosed full prescribing information.

Tarceva in the relapsed or refractory setting

Tarceva in relapsed or refractory stage IIIB/IV NSCLC

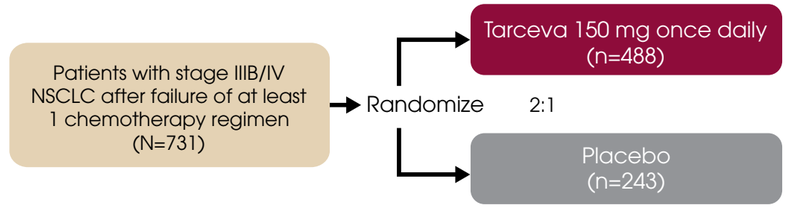
Approved for a broad patient population, irrespective of histology or biomarker status[1]

NCCN guidelines recommend erlotinib as an option for second-line NSCLC therapy based on the results of the BR.21 trial[2]

- Tarceva is the only oral therapy that is FDA approved for the treatment of relapsed or refractory NSCLC in a broad patient population, which includes patients with squamous cell carcinoma.[1]
- Tarceva monotherapy is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.[1]
- Results from two, multicenter, placebo-controlled, randomized, phase III 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.[1]

BR.21 was an international, placebo-controlled, randomized, double-blind phase III study[1]

BR.21 study design[1]



- BR.21 included patients with several different histology types[1]
  – Histologies included squamous cell carcinoma, adenocarcinoma, undifferentiated large-cell, mixed non-small cell, and other.[1]
- Primary end point[1]
  – Overall survival in all patients
- Secondary end points[1,16]
  – Objective response, determined using RECIST criteria
  – Duration of response
  – Progression-free survival
- The intent-to-treat population in the BR.21 trial included patients of varying age, sex, race, ECOG performance status (0-3), smoking status, histology, number of prior regimens (1-3), response to prior chemotherapy, and EGFR IHC status.[1,16]

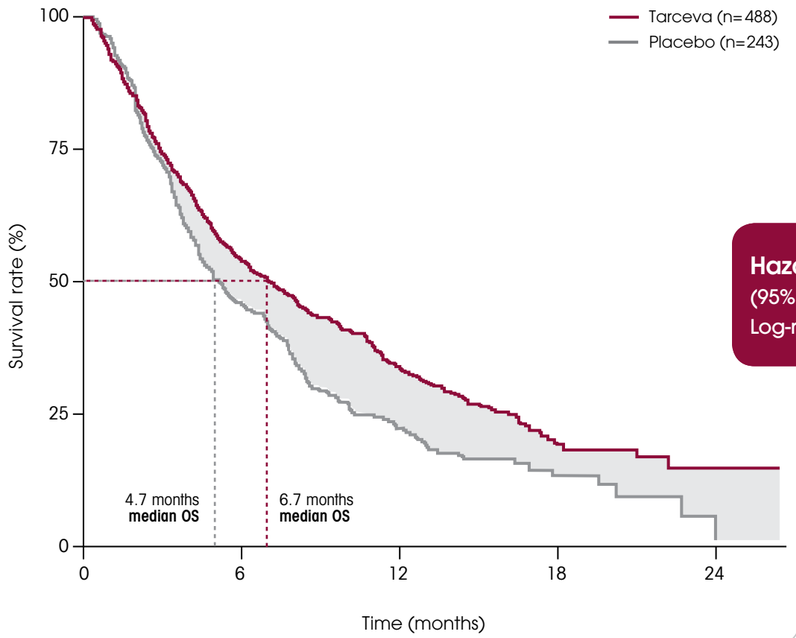
Tarceva® erlotinib tablets

Tarceva in relapsed or refractory stage IIIB/IV NSCLC

Significantly prolonged overall survival in a broad patient population[1]

27% reduction in risk of death[1]

OS in the BR.21 ITT* population



Hazard ratio=0.73
(95% CI=0.61-0.86)
Log-rank *P*<0.001

Important safety information

- International Normalized Ratio (INR) elevations and infrequent reports of bleeding events, including gastrointestinal and nongastrointestinal bleeding, have been reported in clinical studies, some associated with concomitant warfarin administration.[1]
- While receiving Tarceva therapy, women should be advised to avoid pregnancy or breastfeeding.[1]
- The most common adverse reactions in patients with NSCLC receiving single-agent Tarceva were rash and diarrhea.[1]

"[E]rlotinib, an oral tyrosine kinase inhibitor of EGFR, prolongs survival…as compared with placebo, in previously treated patients with non–small-cell lung cancer."[16]

Frances A. Shepherd, MD
University of Toronto
Toronto, Canada

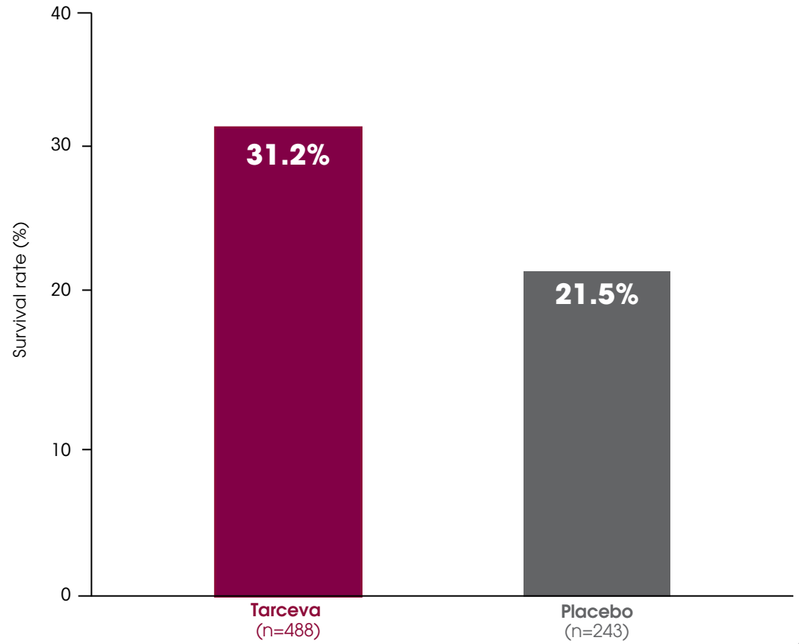
All data are based on Tarceva after failure of at least one prior chemotherapy regimen.
*Intent to treat.

Tarceva in relapsed or refractory stage IIIB/IV NSCLC

Improved 1-year survival in a broad patient population[1]

Improved 1-year survival rate[1]

Patients alive at 1 year in BR.21 ITT* population



- Tarceva increased the 1-year survival rate by nearly 10 percentage points compared to placebo.[1]

*Intent to treat.

Tarceva® erlotinib tablets

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Based on a retrospective exploratory analysis,
with Tarceva in relapsed or refractory stage IIIB/IV NSCLC

Overall survival benefit in the ITT* population extended to squamous cell carcinoma[3]

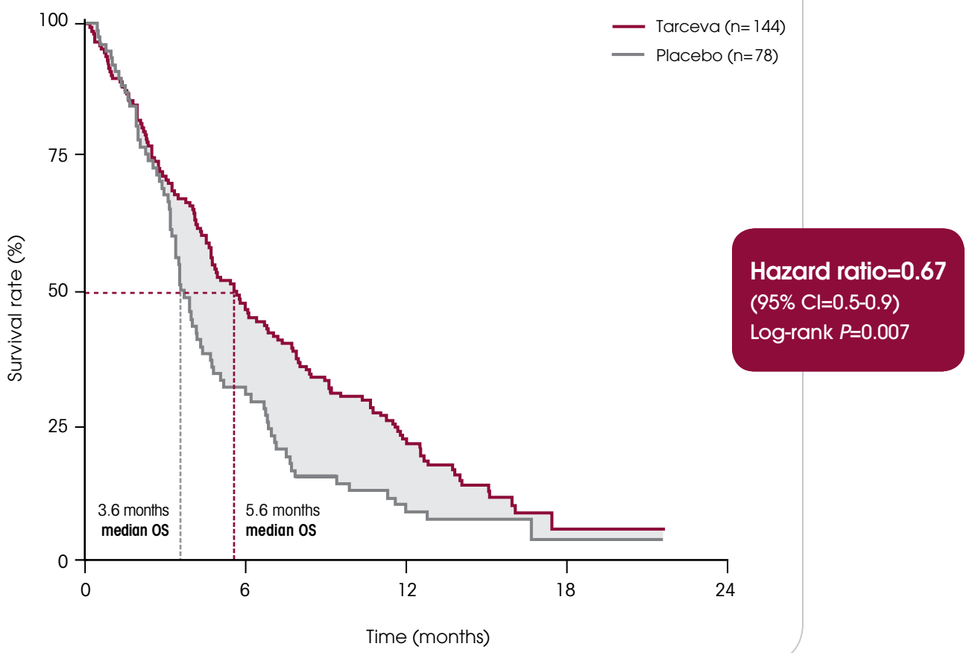
Tarceva significantly prolonged OS in the ITT population[1]

- Tarceva reduced the risk of death in the ITT population by 27% (HR=0.73; 95% CI=0.61-0.86; *P*<0.001; median: 6.7 months with Tarceva vs 4.7 months with placebo).[1]
- Please refer to the Kaplan-Meier curve on page 14.

Tarceva significantly prolonged OS in squamous cell carcinoma, a difficult-to-treat disease[3-5]

33% reduction in risk of death[3]

OS in BR.21 squamous cell carcinoma



Hazard ratio=0.67
(95% CI=0.5-0.9)
Log-rank *P*=0.007

Important safety information

- Warnings and precautions associated with Tarceva, including fatalities, in NSCLC include Interstitial Lung Disease (ILD), renal failure, hepatotoxicity, hepatic impairment, gastrointestinal perforation, bullous and exfoliative skin disorders, ocular disorders, and elevated INR and potential bleeding. Tarceva is pregnancy category D.[1]

*Intent to treat.

Based on a retrospective exploratory analysis,
with Tarceva in relapsed or refractory stage IIIB/IV NSCLC

Overall survival benefit in the ITT* population extended to adenocarcinoma[3]

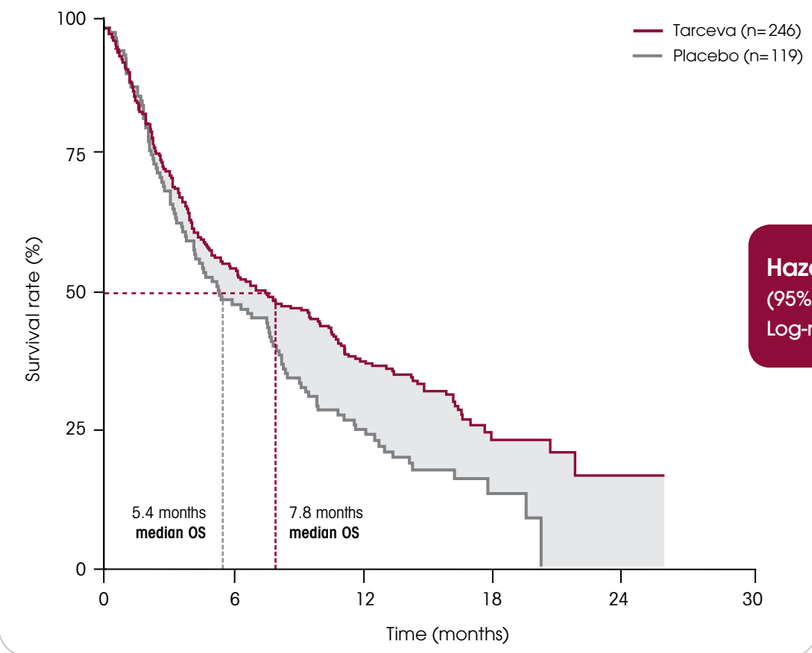
Tarceva significantly prolonged OS in the ITT population[1]

- Tarceva reduced the risk of death in the ITT population by 27% (HR=0.73; 95% CI=0.61-0.86; *P*<0.001; median: 6.7 months with Tarceva vs 4.7 months with placebo).[1]
- Please refer to the Kaplan-Meier curve on page 14.

Tarceva significantly prolonged OS in adenocarcinoma[3]

29% reduction in risk of death[3]

OS in BR.21 adenocarcinoma



Hazard ratio=0.71
(95% CI=0.6-0.9)
Log-rank *P*=0.008

- No benefit was observed in other histologies (n=144); HR=1.04 (95% CI=0.7-1.5; *P*=0.840).[3]

Tarceva® erlotinib tablets

*Intent to treat.

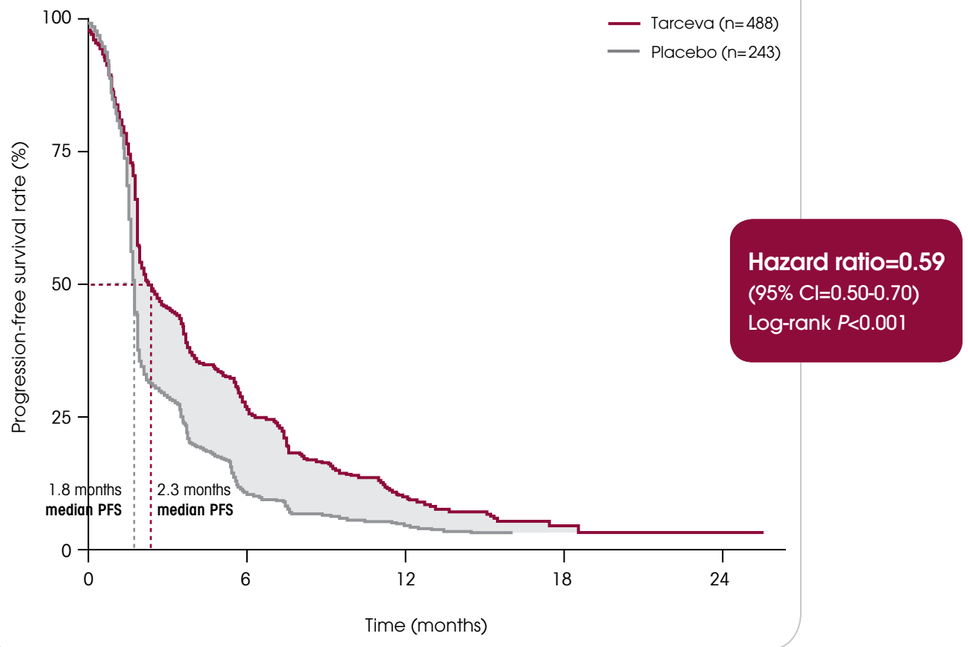
Please see important safety information throughout this piece, on pages 22-23, and in enclosed full prescribing information.

Tarceva in relapsed or refractory stage IIIB/IV NSCLC

Significantly prolonged progression-free survival in a broad patient population[1]

41% reduction in risk of cancer progression or death[1]

PFS in the BR.21 ITT* population



Hazard ratio=0.59
(95% CI=0.50-0.70)
Log-rank *P*<0.001

Important safety information

- The use of Tarceva should be discontinued in patients who develop Interstitial Lung Disease or gastrointestinal perforation. Tarceva should be interrupted or discontinued in patients with severe dehydration; in patients with hepatic failure; in patients with severe bullous, blistering, or exfoliative skin conditions; or in patients with acute/worsening ocular disorders.[1]

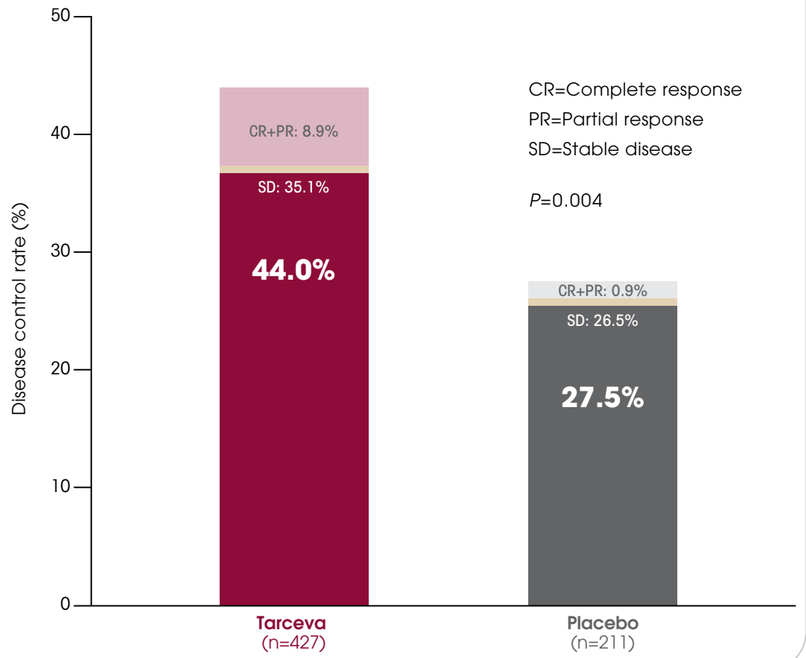
All data are based on Tarceva after failure of at least one prior chemotherapy regimen.
*Intent to treat.

Tarceva in relapsed or refractory stage IIIB/IV NSCLC

Significantly increased disease control rate in a broad patient population[1]

Increased disease control rate[1,3]

CR + PR + SD in the BR.21 ITT* population



- Tarceva significantly increased response rate (CR+PR) compared to placebo (*P*<0.001).[1]
- Median duration of response in patients with measurable disease was 7.9 months with Tarceva (n=38) vs 3.7 months with placebo (n=2).[1,3]

All data are based on Tarceva after failure of at least one prior chemotherapy regimen.
*Intent to treat.

Tarceva® erlotinib tablets

Please see important safety information throughout this piece, on pages 22-23, and in enclosed full prescribing information.

Adverse reactions with Tarceva in relapsed or refractory NSCLC

Serious adverse reactions have occurred with Tarceva; the most common adverse reactions associated with Tarceva are generally manageable[1]

- Serious adverse reactions have been associated with Tarceva therapy.[1]
  - Warnings and precautions associated with Tarceva, including fatalities, in NSCLC include Interstitial Lung Disease (ILD), renal failure, hepatotoxicity, hepatic impairment, gastrointestinal perforation, bullous and exfoliative skin disorders, ocular disorders, and elevated INR and potential bleeding. Tarceva is pregnancy category D.[1]

Most common treatment-related adverse reactions in the BR.21 trial[1]*

Adverse reaction	Tarceva 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
Fatigue	52	14	4	45	16	4
Anorexia	52	8	1	38	5	<1
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
Conjunctivitis	12	<1	0	2	<1	0
Dry skin	12	0	0	4	0	0
Keratoconjunctivitis sicca	12	0	0	3	0	0
Abdominal pain	11	2	<1	7	1	<1

*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.[1]

- The most common adverse reactions in patients receiving Tarceva monotherapy 150 mg for relapsed or refractory NSCLC were grades 1 and 2 rash (~66%) and diarrhea (~47%).[1]

BR.21 trial	Study discontinuation[1]		Dose reduction[1]	
	Rash %	Diarrhea %	Rash %	Diarrhea %
	1	1	6	1

Please see important safety information throughout this piece, on pages 22-23, and in enclosed full prescribing information.

In maintenance and relapsed or refractory stage IIIB/IV NSCLC

Tarceva is the only oral treatment option, providing an alternative to intravenous infusions

Dosing and administration

- The recommended daily dose of Tarceva for NSCLC is **150 mg taken orally on an empty stomach.**[1]
- As one way to help minimize adverse reactions, Tarceva should be taken on an empty stomach at least **one hour before or two hours after eating.**[1]

Dose reduction, interruption, or discontinuation

- In Tarceva-treated patients, dose reduction, interruption, and/or discontinuation may be required to manage the following adverse reactions[1]:
  - Acute onset of new or progressive pulmonary symptoms, such as dyspnea, cough, or fever (pending diagnostic evaluation)
  - Interstitial Lung Disease (ILD)
  - Hepatic failure or gastrointestinal perforation
  - Dehydration in patients at risk for renal failure
  - Severe bullous, blistering, or exfoliative skin conditions
  - Acute/worsening ocular disorders
  - Severe diarrhea in patients who are unresponsive to loperamide or who become dehydrated
  - Severe skin reactions
- When dose reduction is necessary, the Tarceva dose should be reduced in 50-mg decrements.[1]

Active smokers

- Tarceva patients who smoke cigarettes should be advised to stop smoking. Cigarette smoking has been shown to reduce Tarceva exposure.[1]
- The exact dose recommended for smokers is unknown; however, a cautious increase in the dose of Tarceva, not exceeding 300 mg, may be considered while monitoring the patients' safety.[1]
- Efficacy and long-term safety (>14 days) of a dose higher than the recommended starting dose in smokers have not been established. The dose should be reduced immediately to the indicated starting dose if the patient stops smoking.[1]

Managing the most common adverse reactions

- Diarrhea can usually be managed with loperamide. Patients with severe diarrhea who are unresponsive to loperamide should be monitored for dehydration.[1]
- Your Tarceva sales specialist can provide rash management resources, including a rash management algorithm and patient starter kits.

Patient counseling information

If the following signs or symptoms occur, patients should be advised to seek medical advice promptly[1]:

- 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

Tarceva® erlotinib tablets

Important safety information

- There have been reports of serious Interstitial Lung Disease (ILD)-like events, including fatalities, in patients receiving Tarceva. In the NSCLC studies, 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/3rd line study. 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, ILD, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome and lung infiltration. Symptoms started from 5 days to more than 9 months (median 39 days) after initiating Tarceva therapy.
- Tarceva should be interrupted for acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, and fever. If ILD is diagnosed, Tarceva should be discontinued and appropriate treatment instituted as needed.
- 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.
- 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.
- 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.
- Gastrointestinal perforation (including fatalities) has 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. Permanently discontinue Tarceva in patients who develop gastrointestinal perforation.
- 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. Interrupt or discontinue Tarceva treatment if the patient develops severe bullous, blistering or exfoliating conditions.
- Corneal perforation and 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. Interrupt or discontinue Tarceva therapy if patients present with acute/worsening ocular disorders such as eye pain.
- International Normalized Ratio (INR) elevation and infrequent reports of bleeding events, including gastrointestinal and non-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. Some infrequent cases of gastrointestinal bleeding were also associated with concomitant NSAID administration.
- Tarceva is pregnancy category D. When receiving Tarceva, women of childbearing potential should be advised to avoid pregnancy and pregnant women apprised of the potential hazard to a fetus. Adequate contraception methods should be used during therapy, and for at least 2 weeks after completing therapy. Because of the potential for serious adverse reactions in nursing infants from Tarceva, a decision should be made whether to discontinue nursing or discontinue the drug.
- Erlotinib is metabolized predominantly by CYP3A4, and inhibitors of CYP3A4 would be expected to increase exposure. Caution should be used during co-treatment with Tarceva and ketoconazole or other strong CYP3A4 inhibitors such as, but not limited to: atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO) and voriconazole, and grapefruit or grapefruit juice.
- The CYP3A4 inducer rifampicin has been shown to decrease erlotinib AUC, thus, alternate treatments lacking CYP3A4 inducing activity are strongly recommended. In the absence of an alternative treatment, Tarceva dose modification should be considered. 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 CYP3A4 inducers such as, but not limited to: rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital and St. John's Wort.
- Drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and reduce its bioavailability. The concomitant use of proton pump inhibitors, such as omeprazole with Tarceva should be avoided if possible. If patients need to be treated with an H_2-receptor antagonist such as ranitidine, it should be used in a staggered manner. Although the effect of antacids on erlotinib pharmacokinetics has not been evaluated, the antacid dose and the Tarceva dose should be separated by several hours, if an antacid is necessary.
- Patients should be advised to stop smoking while taking Tarceva as cigarette smoking has been shown to reduce erlotinib AUC. However, if patients continue to smoke, a cautious increase in the dose of Tarceva, not to exceed 300 mg, may be considered while monitoring the patient's safety. If the Tarceva dose is adjusted upward, the dose should be reduced immediately to the indicated starting dose upon cessation of smoking.
- The most common adverse reactions in patients with NSCLC receiving single-agent Tarceva 150 mg were rash and diarrhea. In the 2nd/3rd line study, severe rash and diarrhea (9% & 6% NCI-CTC Grades 3/4, respectively) were reported. Rash and diarrhea each resulted in dose reductions (6% and 1%, respectively) and discontinuation in 1% of Tarceva-treated patients. In the maintenance study, severe rash and diarrhea (6.0% & 1.8% NCI-CTC Grades 3/4, respectively) were reported. Rash and diarrhea resulted in dose reductions or interruption (5.1% and 2.8%, respectively) and discontinuation (1.2% and 0.5%, respectively) of Tarceva-treated patients.

Tarceva® erlotinib tablets

Please see important safety information throughout this piece and in enclosed full prescribing information.

Genentech and Astellas have a commitment to provide support for and access to Tarceva treatment for eligible patients

One-on-one telephone support

The Tarceva Patient Support Line offers:

- 24/7 live phone service from registered oncology nurses to patients and their care partners, available at **1-877-TARCEVA** (1-877-827-2382)
- Translation services for a number of languages

Reimbursement support

Tarceva Access Solutions

Tarceva Access Solutions helps resolve access and reimbursement issues for individual patients every day. Our in-house dedicated Specialists help bring patient treatment and practice solutions together. To speak *live* with one of our Specialists, call **(888) 249-4918** or visit **TarcevaAccessSolutions.com**.

Tarceva® erlotinib
Access Solutions™
Treatment made possible.

An Access Solutions specialist can also provide you with information regarding the following programs:

- Genentech® BioOncology Co-Pay Card*
- Genentech® Access to Care Foundation (GATCF)
- GATCF Extension for Medicare Part D Patients
- Tarceva Dose Modification Exchange Program

*Certain restrictions apply.

Assistance for Medicare Part D patients

- Specialty pharmacies may be able to help Medicare Part D patients by providing access to co-pay assistance from independent, public charities.
- Co-pay assistance from independent, public charities may count toward true out-of-pocket expenses (TrOOP) and thus may be able to help support patients in the Medicare coverage gap.

Please see important safety information throughout this piece, on pages 22-23, and in enclosed full prescribing information.

Tarceva is available at retail and specialty pharmacies

Specialty pharmacy services

- Specific services vary among specialty pharmacies. However, most provide disease education or answer questions about the patient's therapy. Contact specialty pharmacies directly to ascertain the services each provides.
- The decision to use the services of a specialty pharmacy should be made solely by the patient and caregiver with guidance from the provider/treatment team.

Services that may be provided by specialty pharmacies

- Prescription delivery
  - Often via overnight delivery service to the location of the patient's choice
- Therapy starter kits
- Therapy education
  - 24/7 hotline to counsel patients on product dosing and administration
  - Side effect management education
  - Proactive monitoring for adherence and adverse events
- Phone contact
  - Directly with patients to provide updates and answer questions about treatment
  - Refill and appointment reminders

References: 1. Tarceva [package insert]. Farmingdale, NY: OSI Pharmaceuticals, LLC, an affiliate of Astellas Pharma US, Inc; 2010. **2.** National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology (NCCN Guidelines™): non-small cell lung cancer (version 3.2011). Fort Washington, PA: NCCN; 2011. **3.** Data on file, OSI Pharmaceuticals, LLC, an affiliate of Astellas Pharma US, Inc. **4.** Stinchcombe TE, Socinski MA. Considerations for second-line therapy of non-small cell lung cancer. *Oncologist.* 2008;13(suppl 1):28-36. **5.** Hensing TA, Schell MJ, Lee JH, Socinski MA. Factors associated with the likelihood of receiving second line therapy for advanced non-small cell lung cancer. *Lung Cancer.* 2005;47(2):253-259. **6.** Rowinsky EK. The erbB family: targets for therapeutic development against cancer and therapeutic strategies using monoclonal antibodies and tyrosine kinase inhibitors. *Annu Rev Med.* 2004;55:433-457. **7.** Herbst RS, Heymach JV, Lippman SM. Molecular origins of cancer: lung cancer. *N Engl J Med.* 2008;359(13):1367-1380. **8.** Cappuzzo F, Magrini E, Ceresoli GL, et al. Akt phosphorylation and gefitinib efficacy in patients with advanced non–small-cell lung cancer. *J Natl Cancer Inst.* 2004;96(15):1133-1141. **9.** Balsara BR, Pei J, Mitsuuchi Y, et al. Frequent activation of AKT in non-small cell lung carcinomas and preneoplastic bronchial lesions. *Carcinogenesis.* 2004;25(11):2053-2059. **10.** Stinchcombe TE, Socinski MA. Treatment paradigms for advanced stage non-small cell lung cancer in the era of multiple lines of therapy. *J Thorac Oncol.* 2009;4(2):243-250. **11.** Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet.* 2009;374(9699):1432-1440. **12.** Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non–small-cell lung cancer. *J Clin Oncol.* 2009;27(4):591-598. **13.** Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol.* 2010;11(6):521-529. **14.** Sun J-M, Park JO, Won Y-W, et al. Who are less likely to receive subsequent chemotherapy beyond first-line therapy for advanced non-small cell lung cancer? Implications for selection of patients for maintenance therapy. *J Thorac Oncol.* 2010;5(4):540-545. **15.** Study showed Tarceva improved progression-free survival as a first-line maintenance therapy for advanced non-small cell lung cancer [press release]. Medical News Today; November 7, 2008. **16.** Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al; National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non–small-cell lung cancer. *N Engl J Med.* 2005;353(2):123-132.

Tarceva® erlotinib tablets

Extending survival *for moments that matter*

Tarceva is approved for a broad patient population, irrespective of histology or biomarker status[1]

- Tarceva monotherapy is indicated for the 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.
- 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.
- Results from two, multicenter, placebo-controlled, randomized, phase III 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.

In the pivotal SATURN trial as maintenance therapy for stage IIIB/IV NSCLC, Tarceva significantly prolonged OS and PFS in a broad patient population[1]

- Tarceva prolonged OS, reducing the risk of death in the ITT* population by 19% (HR=0.81; 95% CI=0.70-0.95; *P*=0.0088; median: 12.0 months with Tarceva vs 11.0 months with placebo).[1]
- Tarceva prolonged PFS, reducing the risk of cancer progression or death in the ITT population by 29%, based on investigator's assessment (HR=0.71; 95% CI=0.62-0.82; *P*<0.0001; median: 2.8 months with Tarceva vs 2.6 months with placebo).[1]

In the pivotal BR.21 trial as treatment for relapsed or refractory stage IIIB/IV NSCLC, Tarceva significantly prolonged OS and PFS in a broad patient population[1]

- Tarceva prolonged OS, reducing the risk of death in the ITT population by 27% (HR=0.73; 95% CI=0.61-0.86; *P*<0.001; median: 6.7 months with Tarceva vs 4.7 months with placebo).[1]
- The OS benefit demonstrated by Tarceva in the ITT population extended to both squamous cell carcinoma and adenocarcinoma, based on a retrospective exploratory analysis.[1,3]
  - Tarceva prolonged OS in squamous cell carcinoma, reducing the risk of death by 33% (HR=0.67; 95% CI=0.5-0.9; *P*=0.007; median: 5.6 months with Tarceva vs 3.6 months with placebo).[3]
  - Tarceva prolonged OS in adenocarcinoma, reducing the risk of death by 29% (HR=0.71; 95% CI=0.6-0.9; *P*=0.008; median: 7.8 months with Tarceva vs 5.4 months with placebo).[3]
- Tarceva prolonged PFS, reducing the risk of cancer progression or death in the ITT population by 41% (HR=0.59; 95% CI=0.50-0.70; *P*<0.001; median: 2.3 months with Tarceva vs 1.8 months with placebo).[1]

Serious adverse reactions have occurred with Tarceva; the most common adverse reactions associated with Tarceva are generally manageable[1]

- Warnings and precautions associated with Tarceva, including fatalities, in NSCLC include Interstitial Lung Disease (ILD), renal failure, hepatotoxicity, hepatic impairment, gastrointestinal perforation, bullous and exfoliative skin disorders, ocular disorders, and elevated INR and potential bleeding. Tarceva is pregnancy category D.[1]
- The most common adverse reactions in patients with NSCLC receiving Tarceva monotherapy 150 mg as maintenance therapy or for relapsed or refractory NSCLC were grades 1 and 2 rash (43.2% in maintenance and ~66% in relapsed/refractory) and diarrhea (18.5% in maintenance and ~47% in relapsed/refractory).[1]

Genentech and Astellas have a commitment to provide support for and access to Tarceva treatment for eligible patients

*Intent to treat.

Genentech A Member of the Roche Group | astellas ONCOLOGY

011D-071-3441

TAR0000086003 5/11

Tarceva® erlotinib tablets

Improving outcomes in first-line advanced pancreatic cancer

Safety and effectiveness have not been studied in pediatric patients.

Extending survival

for moments that matter

Indication and usage

First-line advanced pancreatic cancer

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

Please see important safety information on pages 12-14 and enclosed full prescribing information.

Tarceva® erlotinib tablets

Proven to prolong survival

Extending survival *for moments that matter*

Tarceva plus gemcitabine significantly improved overall survival (OS) throughout the pivotal trial vs gemcitabine alone.[1]

Based on hazard ratio (HR), Tarceva plus gemcitabine improved OS by reducing the risk of death by 19%.[1]

– HR is an important measure of OS in rapidly progressive diseases such as pancreatic cancer, because it encompasses the whole observation period and not just a single point estimate, such as the median.[2]

Tarceva plus gemcitabine improved median OS vs gemcitabine alone: 6.4 months vs 6.0 months, respectively (HR=0.81; 95% CI=0.68-0.97; *P*=0.028).[1]

In PA.3, Tarceva plus gemcitabine showed greater OS rates vs gemcitabine alone at 12 months.[1]

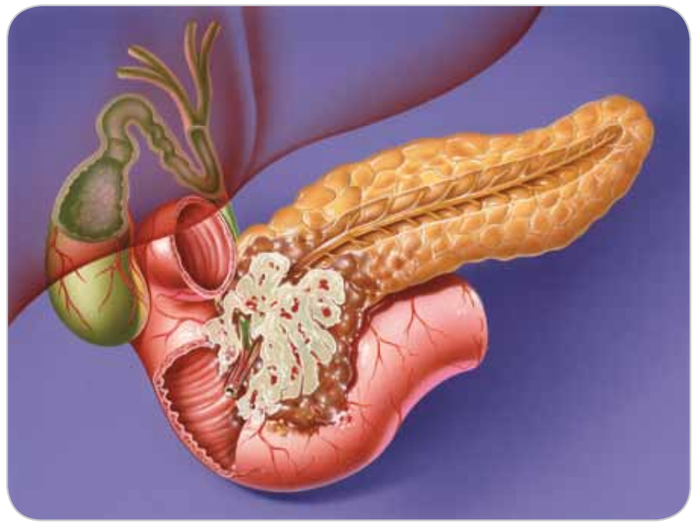
In patients receiving Tarceva plus gemcitabine for pancreatic cancer, myocardial infarction/ischemia, cerebrovascular accident, and microangiopathic hemolytic anemia with thrombocytopenia have occurred, which have included fatalities.[1]

Please see complete pancreatic cancer efficacy data on page 8, important safety information on pages 12-14, and enclosed full prescribing information.

Tarceva® erlotinib tablets

Pancreatic tumors are difficult to treat

Pancreatic cancer invading the duodenum



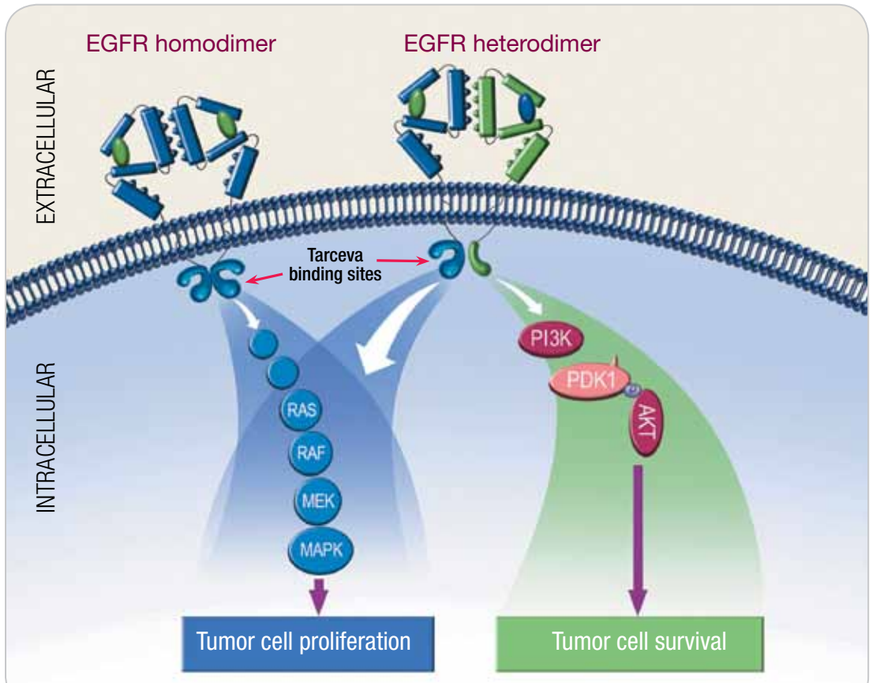
- The predominant form (approximately 90%) of pancreatic cancer is ductal adenocarcinoma.[3]
- Pancreatic ductal adenocarcinoma is characterized by poor vascularization, which creates a barrier for effective cytotoxic delivery.[4,5]
- Tumor cells with overexpression of EGFR or mutation of *EGFR* are more likely to demonstrate resistance to chemotherapy and radiotherapy.[6]

"Exposure of pancreatic cancer cell lines to gemcitabine results in increased phosphorylation and thus activ[a]tion of EGFR."[7]

Bryan A. Faller, MD
Fox Chase Cancer Center
Philadelphia, PA

The combination of an EGFR TKI plus gemcitabine may be synergistic

EGFR has been shown to impact key signaling pathways in pancreatic tumor cells[6,8]



- Tarceva binds to the EGFR homodimer and heterodimer tyrosine kinase domains. This activity may inhibit both tumor cell proliferation and tumor cell survival.[8]
- Exposure of pancreatic cancer cell lines to the combination of an EGFR TKI and gemcitabine resulted in:
  - Enhanced cytotoxicity of gemcitabine[9]
  - Induced apoptosis in tumor cells[10]
- **The mechanism of clinical antitumor action of Tarceva is not fully characterized.[1]**

Tarceva® erlotinib tablets

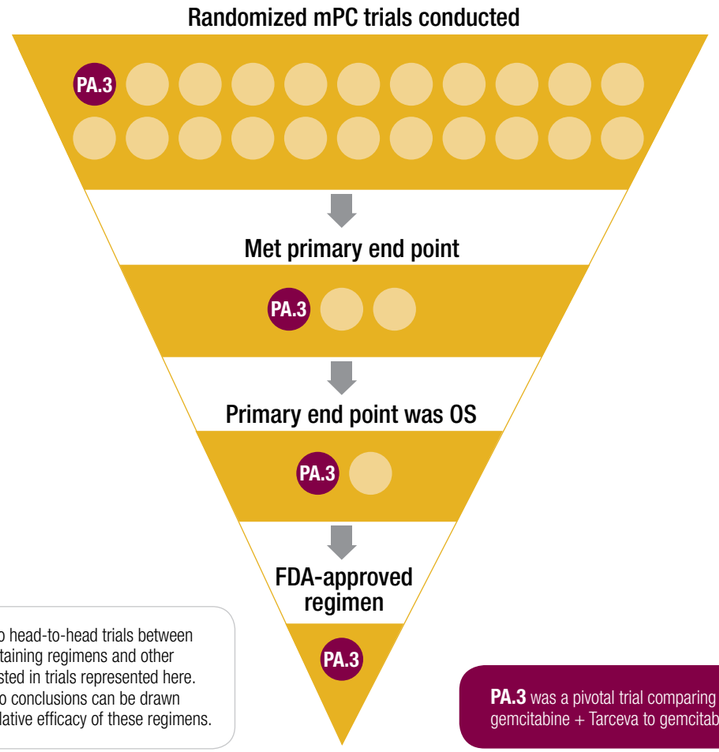
Please see important safety information on pages 12-14 and enclosed full prescribing information.

In first-line advanced pancreatic cancer, the combination of Tarceva plus gemcitabine offers

The first and only FDA-approved combination therapy with a survival benefit[2,3]

Tarceva plus gemcitabine is the only FDA-approved combination therapy that has demonstrated a survival benefit in advanced pancreatic cancer in the last 14 years[1,11-31]

Review of phase III trials in metastatic pancreatic adenocarcinoma over the last 14 years[1,11-31]*



*As of March 2011.

"Erlotinib represents a notable step forward for patients and healthcare providers in a disease with a very poor prognosis."[32]

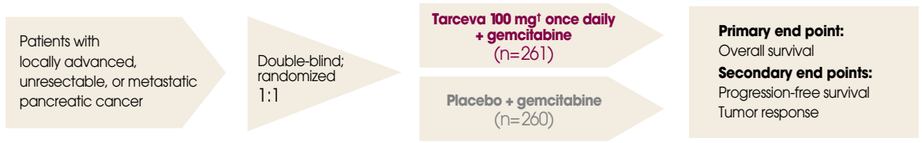
Malcolm J. Moore, MD
Princess Margaret Hospital
Toronto, Canada

Please see important safety information on pages 12-14 and enclosed full prescribing information.

In first-line advanced pancreatic cancer, the combination of Tarceva plus gemcitabine offers

The first and only FDA-approved combination therapy with a survival benefit[2,3]

The landmark PA.3 trial established Tarceva plus gemcitabine as a proven treatment option in pancreatic cancer[2]



† This study also included a Tarceva 150-mg cohort (n=24 randomized patients). Too few patients were treated in the 150-mg cohort to draw conclusions.[1]

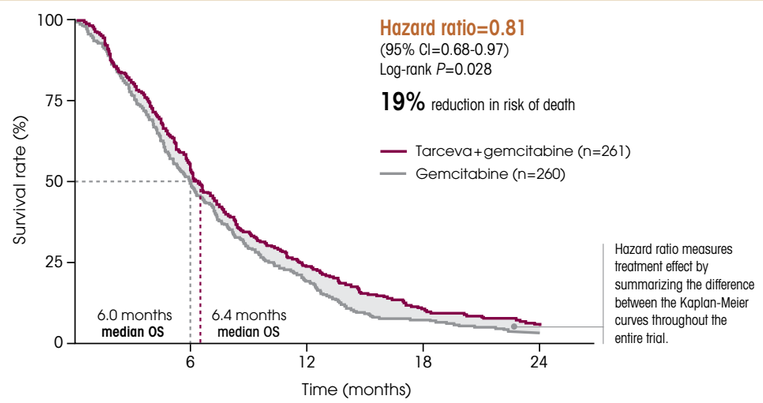
- **Erlotinib plus gemcitabine is recommended as a treatment option for pancreatic cancer in the NCCN guidelines.[3]**
- Tarceva plus gemcitabine is also recommended for the treatment of pancreatic cancer in guidelines set forth by the following:
  - NCI PDQ[33]
  - American Cancer Society[34]
  - Pancreatic Cancer Action Network[35]
  - DRUGDEX Compendium[36]
  - NCCN Drugs and Biologics Compendium[37]
  - Clinical Pharmacology Compendium[36]
- Cases of hepatic failure, hepatorenal syndrome, acute renal failure (all including fatalities), and renal insufficiency have been reported during use of Tarceva.[1]
- Gastrointestinal perforation (including fatalities) has been reported in patients receiving Tarceva.[1]
- 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.[1]

Tarceva® erlotinib tablets

Proven survival in the treatment of advanced pancreatic cancer

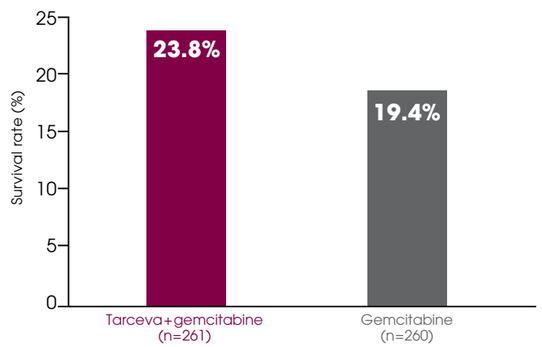
Tarceva plus gemcitabine significantly improved overall survival throughout the pivotal trial vs gemcitabine alone[1]

Tarceva plus gemcitabine improved overall survival[1]



- HR is an important measure of overall survival in rapidly progressive diseases such as pancreatic cancer, because it encompasses the whole observation period and not just a single point estimate, such as the median.[2]

Overall 12-month survival rates in PA.3[1]



- With the addition of Tarceva, more patients lived a full year beyond diagnosis: approximately 1 in 4 with combination therapy vs 1 in 5 with gemcitabine alone.[1]

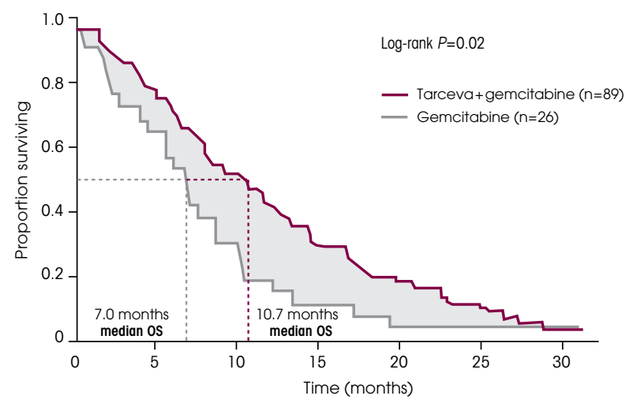
- There have been infrequent reports of serious Interstitial Lung Disease (ILD)-like events, including fatalities, in patients receiving Tarceva.[1]
- Corneal perforation and ulceration have been reported during use of Tarceva.[1]
- When receiving Tarceva therapy, women should be advised against becoming pregnant or breastfeeding. Tarceva is pregnancy category D.[1]

Please see important safety information on pages 12-14 and enclosed full prescribing information.

Proven survival in the treatment of advanced pancreatic cancer

Retrospective data suggest Tarceva-related rash is associated with a clinical benefit

Overall survival in patients with grade 2+ rash[3,37]*



Suggested correlation between rash and overall survival

- Based on a retrospective, exploratory analysis, a strong correlation was observed between the presence of rash and improved survival in the pivotal phase III clinical trial.[2]
- These results must be interpreted with caution but appear to suggest that patients with minimal or no rash (<grade 2) may not benefit from Tarceva plus gemcitabine.[37]
- These data do not support increasing the dosage of Tarceva to cause patients to develop rash.

*Adapted from Senderowicz AM et al, 2007.[38]

"…it may be advantageous to continue treatment of pancreatic cancer patients exhibiting HER-1/EGFR inhibitor–related rash, and provide the appropriate management for the rash based on its severity."[39]

Howard A. Burris III, MD
Sarah Cannon Research Institute
Nashville, TN

Tarceva® erlotinib tablets

Proven to prolong survival

Most common adverse events

- The most common adverse events associated with Tarceva plus gemcitabine were generally mild to moderate and manageable.[1,2]

Most common adverse reactions occurring in Tarceva-treated pancreatic cancer patients: 100-mg cohort[1]

	Tarceva + gemcitabine 1,000 mg/m² IV n=259			Placebo + gemcitabine 1,000 mg/m² 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

Discontinuation due to rash and diarrhea was ≤1%[1]

Discontinuation due to any adverse event was low. Rash and diarrhea each resulted in dose reductions in 2% of patients and discontinuation in up to 1% of patients.[1,2]

- The most common adverse reactions in patients with pancreatic cancer receiving Tarceva 100 mg plus gemcitabine were fatigue, rash, nausea, anorexia, and diarrhea.[1]
- In the Tarceva plus gemcitabine arm, grades 3 or 4 rash and diarrhea were each reported in 5% of Tarceva-treated patients.[1]

Rash management considerations

- Tarceva-related rash is generally mild to moderate and typically develops about 10 days after the start of treatment.[1]
- Employ a proactive approach to managing skin reactions.
- Patients with severe skin reactions may require dose reduction or temporary discontinuation of therapy.[1]

Diarrhea management considerations

- Diarrhea can usually be managed with loperamide.[1]
- Patients with severe diarrhea who are unresponsive to loperamide should be monitored for dehydration, and may require dose reduction or temporary discontinuation of therapy.[1]

The Tarceva Patient Support Line provides patients with information on Tarceva dosing and adverse event management.

- **1-877-TARCEVA (1-877-827-2382)**
- **Staffed 24/7 by oncology certified nurses**

Specialty pharmacies and dosing information

Specialty pharmacy support

Specialty pharmacies offer a range of value-added services that may ease the prescription process and provide education and support to patients with chronic conditions such as cancer. Services provided might include*:

- Reimbursement services
- Reliable assistance for Medicare Part D patients
- Prescription delivery
- Therapy starter kits and education
- Phone contact

Dosing and administration

- The recommended once-daily dose of Tarceva for the treatment of advanced pancreatic cancer is **100 mg taken orally without food** in combination with gemcitabine.[1]
- Tarceva should be taken at least **one hour before or two hours after eating** and on an empty stomach to help ensure that patients obtain consistent plasma levels of the drug.[1]
- 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. 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.[1]
- 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.[1]
- When dose reduction is necessary, the Tarceva dose should be reduced by a 50-mg decrement.[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.[1]

*Contact specialty pharmacies directly to ascertain the services each provides.

Tarceva® erlotinib tablets

Please see important safety information on pages 12-14 and enclosed full prescribing information.

Important safety information

- There have been infrequent reports of serious Interstitial Lung Disease (ILD)-like events, including fatalities, in patients receiving Tarceva. The overall incidence of ILD-like events in Tarceva-treated patients from all studies was approximately 0.7%. In NSCLC, single agent Phase III study incidence was 0.8%—the same as placebo. In pancreatic cancer, in combination with gemcitabine study incidence was 2.5% in the Tarceva plus gemcitabine arm vs. 0.4% in the placebo plus gemcitabine arm.
- Reported diagnoses in patients suspected of having ILD-like events included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, ILD, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome and lung infiltration. Symptoms started from 5 days to more than 9 months (median 39 days) after the initiation of Tarceva therapy.
- Tarceva should be interrupted for acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, and fever, and if ILD is diagnosed, Tarceva should be discontinued.
- 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.
- 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.
- 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.
- Gastrointestinal perforation (including fatalities) has 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. Permanently discontinue Tarceva in patients who develop gastrointestinal perforation.

Important safety information (continued)

- 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. Interrupt or discontinue Tarceva treatment if the patient develops severe bullous, blistering or exfoliating conditions.
- In the pancreatic cancer trial, myocardial infarction/ischemia occurred in 2.3% of patients (6 patients) in the Tarceva plus gemcitabine arm vs. 1.2% (3 patients) in the placebo plus gemcitabine arm. One patient in the Tarceva plus gemcitabine arm and one patient in the placebo plus gemcitabine arm died due to myocardial infarction.
- In the pancreatic cancer trial, 2.3% of patients (6 patients) in the Tarceva plus gemcitabine arm developed cerebrovascular accidents vs. no cerebrovascular accidents in the placebo plus gemcitabine arm. One of the cerebrovascular accidents was hemorrhagic and fatal.
- In the pancreatic cancer trial, 0.8% of patients (2 patients) developed microangiopathic hemolytic anemia with thrombocytopenia in the Tarceva plus gemcitabine arm vs. no cases in the placebo plus gemcitabine arm.
- Corneal perforation and 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. Interrupt or discontinue Tarceva therapy if patients present with acute/worsening ocular disorders such as eye pain.
- When receiving Tarceva, women of childbearing potential should be advised to avoid pregnancy and pregnant women apprised of the potential risks to the fetus. Tarceva should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the fetus. Women receiving Tarceva should be advised against breastfeeding. Tarceva is pregnancy category D.
- International Normalized Ratio (INR) elevation and infrequent reports of 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. Some infrequent cases of gastrointestinal bleeding were also associated with concomitant NSAID administration.
- The potent CYP3A4 inhibitor ketoconazole has been shown to increase erlotinib AUC; thus, caution should be used during co-treatment with Tarceva and ketoconazole or other strong CYP3A4 inhibitors such as, but not limited to: atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO) and voriconazole, and grapefruit or grapefruit juice. When Tarceva was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2, the erlotinib AUC increased by 39%.

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Important safety information (continued)

- The CYP3A4 inducer rifampicin has been shown to decrease erlotinib AUC, thus, alternate treatments lacking CYP3A4 inducing activity are strongly recommended. In the absence of an alternative treatment, Tarceva dose modification should be considered. 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 CYP3A4 inducers such as, but not limited to: rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital and St. John's Wort.
- Drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and reduce its bioavailability. Co-administration of Tarceva with omeprazole, a proton pump inhibitor, decreased the erlotinib AUC by 46%. Increasing the dose of Tarceva when co-administered with such agents is not likely to compensate for the loss of exposure. The concomitant use of proton pump inhibitors with Tarceva should be avoided if possible.
- Smokers should be advised to stop smoking while taking Tarceva as plasma concentrations of erlotinib are reduced due to the effect of cigarette smoking. However, if they continue to smoke, cautious increase in the dose of Tarceva, not to exceed 300 mg, may be considered while monitoring the patient's safety. If the Tarceva dose is adjusted upward, the dose should be reduced immediately to the indicated starting dose upon cessation of smoking.
- NCI-CTC Grade 3 conjunctivitis and keratitis have been reported infrequently in patients receiving Tarceva therapy. Corneal ulcerations may also occur.
- The most common adverse reactions in patients with pancreatic cancer receiving Tarceva 100 mg plus gemcitabine were fatigue, rash, nausea, anorexia and diarrhea. Severe rash and diarrhea (5% and 5% NCI-CTC Grades 3–4, respectively) were reported. Rash and diarrhea each resulted in dose reductions in 2% of patients, and discontinuation in up to 1% of patients receiving Tarceva plus gemcitabine.

Please see enclosed full prescribing information.

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Improving outcomes in first-line advanced pancreatic cancer

Extending survival for moments that matter

OVERALL SURVIVAL AS PRIMARY END POINT

Tarceva plus gemcitabine is the only FDA-approved combination therapy that has demonstrated a survival benefit in advanced pancreatic cancer in the last 14 years.[11-31] Tarceva plus gemcitabine improved median OS vs gemcitabine alone: 6.4 months vs 6.0 months, respectively (HR=0.81; 95% CI=0.68-0.97; *P*=0.028).[1]

A RECOMMENDED TREATMENT OPTION

Erlotinib plus gemcitabine is FDA approved and recommended as a treatment option in the NCCN guidelines for the first-line treatment of advanced pancreatic cancer.[3]

19% REDUCTION IN THE RISK OF DEATH

Tarceva plus gemcitabine achieved a hazard ratio of 0.81.[1] HR is an important measure of overall survival in rapidly progressive diseases such as pancreatic cancer, because it encompasses the whole observation period and not just a single point estimate, such as the median.[2]

ADVERSE REACTIONS

The most common adverse reactions in patients with pancreatic cancer receiving Tarceva 100 mg plus gemcitabine were fatigue, rash, nausea, anorexia, and diarrhea.[1]

RESOURCES

Significant resources exist to support reimbursement and help ensure oral adherence, including:

- Tarceva Access Solutions
  1-888-249-4918 (weekdays 6 AM-5 PM PST)
  www.TarcevaAccessSolutions.com

Tarceva® erlotinib Access Solutions™ Treatment made possible.

- The Tarceva Patient Support Line
  1-877-TARCEVA (1-877-827-2382)
  Nurses staffed 24/7

Please see important safety information on pages 12-14 and enclosed full prescribing information.

Visit Tarceva.com for additional information and resources.

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