

Tarceva rash management guide



Safety and effectiveness have not been studied in pediatric patients.

Indications

Non-small cell lung cancer (NSCLC)

Tarceva monotherapy is indicated for:

- the maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer (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.

Pancreatic cancer

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

Please see important safety information on pages 14-15 and enclosed full prescribing information.

 **Tarceva**[®]
erlotinib
tablets

Extending survival for moments that matter

NSCLC maintenance study efficacy results

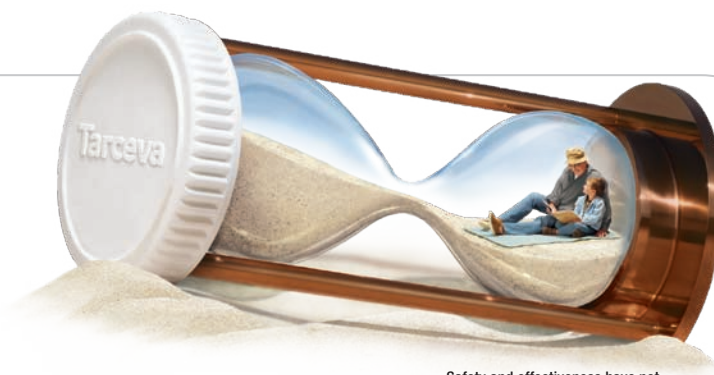
- As maintenance therapy in the SATURN trial, which evaluated Tarceva (n=438) vs placebo (n=451) in a broad (ITT) patient population of stage IIIB/IV NSCLC patients, Tarceva significantly improved:
 - OS with a 19% reduction in the risk of death (HR=0.81; 95% CI=0.70-0.95; $P=0.0088$; median: 12.0 months with Tarceva vs 11.0 months with placebo)¹
 - PFS based on investigator's assessment with a 29% reduction in the risk of cancer progression or death (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

Relapsed or refractory NSCLC efficacy results

- In a broad (ITT) patient population of relapsed or refractory stage IIIB/IV NSCLC patients in the BR.21 trial, which evaluated Tarceva (n=488) vs placebo (n=243), Tarceva significantly improved:
 - OS with a 27% reduction in the risk of death (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
 - PFS with a 41% reduction in the risk of cancer progression or death (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

First-line pancreatic cancer efficacy results

- In advanced pancreatic cancer patients as first-line therapy in the PA.3 trial, which evaluated Tarceva plus gemcitabine (n=261) vs gemcitabine alone (n=260), Tarceva plus gemcitabine significantly improved:
 - OS with a 19% reduction in the risk of death (HR=0.81; 95% CI=0.68-0.97; $P=0.028$; median: 6.4 months with Tarceva plus gemcitabine vs 6.0 months with gemcitabine alone)¹
 - PFS with a 24% reduction in the risk of cancer progression or death (HR=0.76; 95% CI=0.64-0.92; $P=0.006$; median: 3.8 months with Tarceva plus gemcitabine vs 3.5 months with gemcitabine alone)¹



Safety and effectiveness have not been studied in pediatric patients.

The most common adverse reactions associated with Tarceva are generally manageable¹

- The most common adverse reactions in patients 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
- The most common adverse reactions in patients with pancreatic cancer receiving Tarceva 100 mg plus gemcitabine were grades 1 and 2 rash (64%), fatigue (57%), nausea (53%), anorexia (~45%), and diarrhea (~42%).¹
- Other serious adverse reactions have been associated with Tarceva therapy.¹
 - Warnings and precautions associated with Tarceva in NSCLC and Tarceva plus gemcitabine in pancreatic cancer include Interstitial Lung Disease (ILD), renal failure, hepatotoxicity, hepatic impairment, gastrointestinal perforation, bullous and exfoliative skin disorders, myocardial infarction/ischemia, cerebrovascular accident, microangiopathic hemolytic anemia with thrombocytopenia, ocular disorders, and elevated INR and potential bleeding. Tarceva is pregnancy category D.¹

Understanding Tarceva-related rash

This brochure includes information intended to help you manage the common side effects associated with Tarceva, particularly rash. Rash management information is included in the Tarceva prescribing information. However, other experts, including those at your institution, may have a different approach to managing Tarceva-related rash.

Specifically, this brochure highlights:

- Descriptions of rash characteristics
- Rash management information
- A sample skin reaction management algorithm
- Dose adjustment guidelines
- The importance of taking Tarceva on an empty stomach (one hour before or two hours after eating)

There are currently no data from well-controlled clinical trials regarding the treatment of Tarceva-related rash.

Information on managing the other common side effects associated with Tarceva is listed at the end of this brochure.

This brochure is provided solely for your information and is not intended as Genentech or OSI recommendations, nor should it be construed as a substitute for independent medical judgment. The healthcare provider should determine what is appropriate for each patient.

Rash

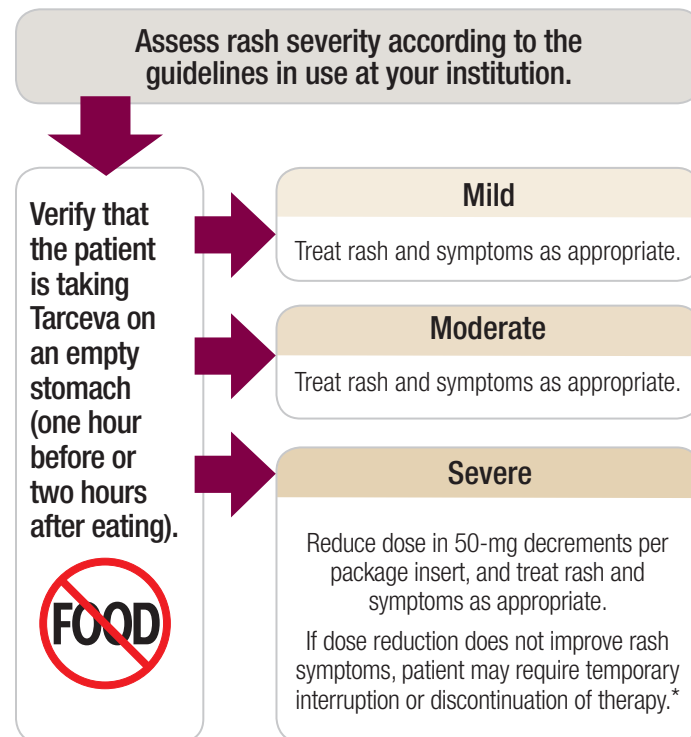
- Tarceva is a tyrosine kinase inhibitor. Although the etiology is unknown, Tarceva has been associated with the development of rash.¹ See pages 6 and 7 for suggestions on managing Tarceva-related rash.

Rash characteristics

- In pivotal trials for Tarceva in advanced NSCLC and advanced pancreatic cancer, rash was among the most common side effects, reported in¹:
 - 49.2% of patients in the SATURN trial for maintenance therapy in NSCLC
 - 75% of patients in the BR.21 trial for relapsed or refractory NSCLC therapy
 - 69% of patients in the PA.3 trial for first-line pancreatic cancer therapy
- Tarceva-related rash was associated with discontinuation and dose reduction or interruption as follows¹:
 - 1.2% discontinuation and 5.1% dose reduction or interruption in the SATURN trial for maintenance therapy in NSCLC
 - 1% discontinuation and 6% dose reduction in the BR.21 trial for relapsed or refractory NSCLC therapy
 - Up to 1% discontinuation and 2% dose reduction in the PA.3 trial for first-line pancreatic cancer therapy
- Typically, the rash develops within 2 weeks after the start of treatment. In the pivotal trials, rash appeared between^{1,2}:
 - 1 and >30 days in the SATURN trial for maintenance therapy in NSCLC
 - 1 and 113 days in the BR.21 trial for relapsed or refractory NSCLC therapy
 - 1 and 421 days in the PA.3 trial for first-line pancreatic cancer therapy
- Tarceva-related rash was generally mild to moderate and affected skin areas above the waist.^{1,3}
- The occurrence of rash may resolve spontaneously. Although rash is commonly referred to as “acneiform,” it is not acne and should not be treated as acne.³

Patient rash assessment

The algorithm and general rash management considerations featured on pages 7 through 9 were developed by medical advisers at a company-sponsored advisory board meeting in October 2006. These recommendations were subsequently published.⁴ The medical advisers were paid by Genentech USA, Inc., OSI Pharmaceuticals, Inc., and F. Hoffmann-La Roche Ltd. to participate in the forum. Rash management information is included in the Tarceva prescribing information. However, other medical experts, including those at your institution, may have a different approach to managing rash.



Rash grading and sample rash management algorithm⁴

General rash management considerations

- Employ a proactive approach to managing skin reactions.⁴
- Suggest patients use a thick, alcohol-free emollient cream on dry areas of the body.⁴
- Suggest patients use a sunscreen of SPF 15 or higher, preferably containing zinc oxide or titanium dioxide.⁴
- For patients who present with rash, verify appropriate administration and consider the following algorithm in a stepwise manner.⁴

Rash grading and rash management are subjective and may vary according to the healthcare professional's judgment, institutional guidelines, and patients' symptoms. The grading methodology is not based on the NCI-CTC grading criteria. For patients in clinical trials, please follow adverse reactions grading, including rash criteria, per the trial's protocol.

This intervention information reflects the opinion of a select group of medical experts and should not be construed as evidence-based guidelines or as Genentech or OSI recommendations. This information is not intended to serve as a substitute for independent medical judgment.

* Activities of daily living.

[†] The use of these medications for the management of rash may be outside the FDA-labeled indications for these products. For complete information regarding the safety and use of these medications, please see the full prescribing information for each product.

[‡] The use of topical steroids should be employed in a pulse manner based on your institution's guidelines.

Rash severity grading

Mild

- Generally localized
- Minimally symptomatic
- No impact on ADL*
- No sign of superinfection



Moderate

- Generalized
- Mild symptoms (eg, pruritus, tenderness)
- Minimal impact on ADL*
- No sign of superinfection



Severe

- Generalized
- Severe symptoms (eg, pruritus, tenderness)
- Significant impact on ADL*
- Potential for superinfection



Intervention[†]

Continue EGFR inhibitor at current dose, and monitor for change in severity

No treatment OR

Topical hydrocortisone 1% or 2.5% cream[‡] and/or clindamycin 1% gel

Reassess after 2 weeks; if reactions worsen or do not improve, proceed to next step

Continue EGFR inhibitor at current dose, and monitor for change in severity; continue treatment of skin reaction with the following:

Hydrocortisone 2.5% cream[‡] or clindamycin 1% gel or pimecrolimus 1% cream PLUS doxycycline 100 mg BID or minocycline 100 mg BID

Reassess after 2 weeks; if reactions worsen or do not improve, proceed to next step

Reduce EGFR-inhibitor dose per label, and monitor for change in severity; continue treatment of skin reaction with the following:

Hydrocortisone 2.5% cream[‡] or clindamycin 1% gel or pimecrolimus 1% cream PLUS doxycycline 100 mg BID or minocycline 100 mg BID PLUS methylprednisolone dose pack

Reassess after 2 weeks; if reactions worsen, dose interruption or discontinuation may be necessary

Photos courtesy of Pamela Hallquist Viale, RN, MS, AOCNP

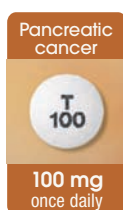
Dosing and administration guidelines

Dose reduction or interruption

- In Tarceva-treated patients, dose reduction and/or interruption may be required for the following adverse reactions¹:
 - Acute onset of new or progressive pulmonary symptoms, such as dyspnea, cough, or fever (pending diagnostic evaluation)
 - 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

Treatment discontinuation

- In Tarceva-treated patients, treatment discontinuation may be required for the following adverse reactions¹:
 - Interstitial Lung Disease (ILD) (appropriate treatment should be instituted as necessary)
 - Hepatic failure or gastrointestinal perforation
 - Severe bullous, blistering, or exfoliative skin conditions
 - Acute/worsening ocular disorders
- To allow for dose reduction when appropriate, Tarceva is also available in 100-mg and 25-mg strengths.¹
- When dose reduction is necessary, Tarceva should be reduced by 50-mg decrements.¹



Do not take
Tarceva with food

- 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

Offsetting the cost of a dose adjustment

- Tarceva offers a Dose Modification Exchange Program that replaces, free of charge, the remaining tablets in the existing prescription with tablets of the reduced dose. For assistance, contact Genentech Customer Service at **1-800-551-2231** or **customer.service@gene.com**.

Common Tarceva-related adverse reactions

The most common adverse reactions associated with Tarceva are generally manageable¹

- The most common adverse reactions in patients 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
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- Other serious adverse reactions have been associated with Tarceva therapy.¹
 - Warnings and precautions associated with Tarceva in NSCLC and Tarceva plus gemcitabine in pancreatic cancer include Interstitial Lung Disease (ILD), renal failure, hepatotoxicity, hepatic impairment, gastrointestinal perforation, bullous and exfoliative skin disorders, myocardial infarction/ischemia, cerebrovascular accident, microangiopathic hemolytic anemia with thrombocytopenia, ocular disorders, and elevated INR and potential bleeding. Tarceva is pregnancy category D.¹

The majority of these reactions were mild to moderate.¹ Below are some possible approaches to managing these adverse reactions.

Advanced NSCLC

Rash

- See pages 7 through 9 for information on the management of Tarceva-related rash.
- Patients should be instructed to take Tarceva on an empty stomach **at least one hour before or two hours after the ingestion of food.**¹
- Suggest patients use a thick, alcohol-free emollient cream on dry areas of the body.⁴
- Suggest patients use a sunscreen of SPF 15 or higher, preferably containing zinc oxide or titanium dioxide.⁴

Diarrhea

- Diarrhea is most likely to occur within the first week or two of Tarceva treatment.¹
- Diarrhea can usually be managed with loperamide. Patients with severe diarrhea who are unresponsive to loperamide should be monitored for dehydration.¹

Advanced pancreatic cancer

Fatigue

- Short rests throughout the day may help patients ward off fatigue.⁵

Rash

- As noted in the Advanced NSCLC section.

Nausea

- Nausea may be managed with an antiemetic.⁵

Anorexia

- Modifications in diet may help offset the loss of appetite.⁵

Diarrhea

- As noted in the Advanced NSCLC section.

References: **1.** Tarceva [package insert]. Melville, NY: OSI Pharmaceuticals Inc; 2010. **2.** Data on file, OSI Pharmaceuticals Inc. **3.** Pérez-Soler R, Delord JP, Halpern A, et al. HER1/EGFR inhibitor-associated rash: future directions for management and investigation outcomes from the HER1/EGFR Inhibitor Rash Management Forum. *Oncologist*. 2005;10(5):345-356. **4.** Lynch TJ Jr, Kim ES, Eaby B, Garey J, West DP, Lacouture ME. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. *Oncologist*. 2007;12(5):610-621. **5.** National Cancer Institute. *Chemotherapy and You: A Guide to Self-Help During Cancer Treatment*. Bethesda, MD: National Cancer Institute, National Institutes of Health, US Dept of Health and Human Services; 2003. NIH publication 03-1136.

Important safety information

- There have been reports of serious Interstitial Lung Disease (ILD)-like events, including fatalities, in patients receiving Tarceva for treatment of NSCLC, pancreatic cancer or other advanced solid tumors. Tarceva therapy 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 hepatic failure, hepatorenal syndrome, acute renal failure (all including fatalities), and renal insufficiency have been reported during use of Tarceva. Treatment with Tarceva should be used with extra caution in patients with total bilirubin $> 3 \times$ ULN. Tarceva dosing should be interrupted or discontinued if changes in liver function are severe. Patients should be closely monitored during therapy with Tarceva.
- Gastrointestinal perforation (including fatalities) has been reported in patients receiving Tarceva. 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.
- In the pancreatic cancer trial, other serious adverse reactions associated with Tarceva plus gemcitabine and which may have included fatalities, were myocardial infarction/ischemia, cerebrovascular accident and microangiopathic hemolytic anemia with thrombocytopenia.
- Corneal perforation and ulceration have been reported during use of Tarceva. 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. Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.
- Tarceva is pregnancy category D. When receiving Tarceva therapy, women should be advised to avoid pregnancy or breastfeeding.
- 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.
- 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 important safety information on pages 14-15 and enclosed full prescribing information.

Visit Tarceva.com for additional information and resources.



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