The most common adverse events for patients taking Tarceva for advanced NSCLC in clinical studies were rash and diarrhea, while the most common adverse events for patients taking Tarceva plus gemcitabine for advanced pancreatic cancer in clinical studies were fatigue, rash, nausea, anorexia, and diarrhea.1 The majority of these events were mild to moderate.2 Below are some possible approaches to managing these adverse events.

**Advanced NSCLC**

**Rash**
- See pages 6 and 7 for information on the management of Tarceva-related rash.
- Patients should be instructed to take Tarceva at least one hour before or two hours after the ingestion of food.1,2
- Suggest patients use a thick, alcohol-free emollient cream on dry areas of the body.1,2
- Suggest patients use a sunscreen of SPF 15 or higher, preferably containing zinc oxide or titanium dioxide.1,2
- Rash is most likely to occur within the first week or two of Tarceva treatment.1,2
- In the Tarceva pivotal clinical trial, patients who experienced NCI-CTC Grade 2 diarrhea were managed with loperamide.1,2

**Diarrhea**
- Diarrhea is most likely to occur within the first week or two of Tarceva treatment.1,2
- 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.2
- Oral perforation and ulceration have been reported during use of Tarceva. Irritants or discontinuation of Tarceva therapy if patients present with acute/worsening ocular disorders such as eye pain.2
- When receiving Tarceva therapy, women should be advised against becoming pregnant or breastfeeding. Tarceva is pregnancy category D.1,5
- Tarceva in combination with gemcitabine is recommended in that setting.1,5

**Advanced pancreatic cancer**

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

**Rash**
- As noted above.1,2

**Nausea**
- Nausea may be managed with an antiemetic.1,2

**Anorexia**
- Modifications in diet may help offset the loss of appetite.1,2

**Diarrhea**
- As noted above.1,2

**Important safety information**

There have been infrequent reports of serious Interstitial Lung Disease (ILD) like events, including fatalities, in patients receiving Tarceva for treatment of NSCLC, pancreatic cancer or other advanced solid tumors. In the event of an acute onset of new or progressive, unexplained pulmonary symptoms such as dyspnea, cough and fever, Tarceva therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, Tarceva should be discontinued and appropriate treatment instituted as needed.

- Cases of hepatic failure, hepatorenal syndrome, acute renal failure (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 > 1.5 x ULN. Tarceva dosing should be interrupted or discontinued if changes in liver function tests 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 in some cases fatal. Tarceva therapy should be interrupted if the patient develops severe bullous, blistering or exfoliative skin conditions.1,2
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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.
- Importance of taking Tarceva without food (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. See pages 6 and 7 for suggestions on managing Tarceva-related rash.

Rash characteristics

- In BR.21 and PA.3, the pivotal clinical trials for Tarceva in advanced NSCLC and advanced pancreatic cancer, respectively, rash was among the most common side effects, reported in about 75% of patients with advanced NSCLC and about 69% of patients with advanced pancreatic cancer. In BR.21 and PA.3, respectively.
- Tarceva-related rash was associated with 1% discontinuation in both pivotal clinical trials; 6% and 2% of Tarceva-treated patients required dose reductions in BR.21 and PA.3, respectively.
- Typically, the rash develops about 8 to 10 days after the start of treatment. In general, rash may appear between 1 and 113 days.
- Tarceva-related rash generally was mild to moderate and affected skin areas above the waist.
- The occurrence of rash may be intermittent. Although rash is commonly referred to as “acneiform,” it is not acne and should not be treated as acne.
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.
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- A sample skin reaction management algorithm.
- Dose adjustment guidelines.
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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.

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Rash characteristics

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- The occurrence of rash may be intermittent. Although rash is commonly referred to as “acneiform,” it is not acne and should not be treated as acne.\(^3\)

Please see important safety information on back cover and enclosed full prescribing information.
Patient rash assessment

The algorithm and general rash management considerations described on pages 6 and 7 were developed by medical advisors at a company-sponsored advisory board meeting in 2006. These recommendations were subsequently published. The medical advisors were paid by Genentech USA, Inc., OSI Pharmaceuticals, Inc., and Hoffman-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.

Important safety information

Common Tarceva-related adverse events

The most common adverse events in patients taking Tarceva for advanced NSCLC in clinical studies were rash and diarrhea, while the most common adverse events for patients taking Tarceva plus gemcitabine for advanced pancreatic cancer in clinical studies were fatigue, rash, nausea, anorexia, and diarrhea. The majority of these events were mild to moderate. Below are some possible approaches to managing these adverse events.

Advanced NSCLC

Rash
- See pages 6 and 7 for information on the management of Tarceva-related rash.
- Patients should be instructed to take Tarceva at least one hour before or two hours after the ingestion of food.
- Suggest patients use a thick, alcohol-free emollient cream on dry areas of the body.
- Suggest patients use a sunscreen of SPF 15 or higher, preferably containing zinc oxide or titanium dioxide.

Diarrhea
- Diarrhea is most likely to occur within the first week or two of Tarceva treatment.
- In the Tarceva pivotal clinical trial, patients who experienced NCI-CTC Grade 2 diarrhea were managed with loperamide.

Advanced pancreatic cancer

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

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

Diabetes
- As noted above.

Nausea
- Nausea may be managed with an antemetic.

Analgesia
- As noted above.

Common Tarceva-related adverse events

- There have been infrequent reports of serious interstitial lung disease (ILD)–like events. Including fatalities, in patients receiving Tarceva for treatment of NSCLC, pancreatic cancer or other advanced solid tumors. In the event of an acute onset of new or progressive, unexplained pulmonary symptoms such as dyspnea, cough and fever, Tarceva therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, Tarceva should be discontinued and appropriate treatment instituted as needed.
- Cases of hepatic failure, hepatorenal syndrome, acute renal failure (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 > 1 x ULN. Tarceva dosing should be interrupted or discontinued if changes in liver function are severe. Patients should be closely monitored during therapy with Tarceva.
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- Bullous, blistering and exfoliative skin conditions have been reported including cases suggestive of Stevens Johnson syndrome/toxic epidermal necrolysis, which in some cases was fatal. Interrupt or discontinue Tarceva treatment if the patient develops severe bullous, blistering or exfoliative skin disorders.
- In the pancreatic cancer trial, other serious adverse reactions associated with Tarceva plus gemcitabine and which may have included fatalities, were myocardial infarction/infarction, 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.
- When receiving Tarceva therapy, women should be advised against becoming pregnant or breastfeeding. Tarceva is pregnancy category D.
- See pages 6 and 7 for information on the management of Tarceva-related rash.
- Patients should be instructed to take Tarceva at least one hour before or two hours after the ingestion of food.
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- Diarrhea is most likely to occur within the first week or two of Tarceva treatment.
- In the Tarceva pivotal clinical trial, patients who experienced NCI-CTC Grade 2 diarrhea were managed with loperamide.

Advanced pancreatic cancer

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Diabetes
- As noted above.

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- In the Tarceva pivotal clinical trial, patients who experienced NCI-CTC Grade 2 diarrhea were managed with loperamide.

Important safety information

Rash Management Guide

Indications and usage

Second-line advanced NSCLC

Tarceva monotherapy is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) 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 and cisplatin-based chemotherapy, and its use is not recommended in that setting.

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.

Visit Tarceva.com for additional information and resources.

Models are for illustrative purposes only.

Please see enclosed full prescribing information.
In an NSCLC trial and a pancreatic cancer trial, up to 1% of patients receiving Tarceva discontinued due to rash.

Assess rash severity according to the guidelines in use at your institution.

Verify that the patient is taking Tarceva without food (one hour before or two hours after a meal).

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat rash and symptoms as appropriate.</td>
<td>Treat rash and symptoms as appropriate.</td>
<td>Reduce dose in 50-mg decrements per package insert and treat rash and symptoms as appropriate.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If dose reduction does not improve rash symptoms, patient may require temporary interruption of therapy.</td>
</tr>
</tbody>
</table>

* In an NSCLC trial and a pancreatic cancer trial, up to 1% of patients receiving Tarceva discontinued due to rash.
Rash grading and sample rash management algorithm

General rash management considerations

- Employ a proactive approach in managing skin reactions.
- Suggest patients use a thick, alcohol-free emollient cream on dry areas of the body.\(^3\)
- Suggest patients use a sunscreen of SPF 15 or higher, preferably containing zinc oxide or titanium dioxide.\(^3,5\)
- If patient presents with rash, verify appropriate administration and consider the following algorithm in a stepwise manner.

<table>
<thead>
<tr>
<th>Rash severity grading</th>
<th>Intervention(^\dagger)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td></td>
</tr>
<tr>
<td>• Generally localized</td>
<td>Continue EGFR inhibitor at current dose and monitor for change in severity</td>
</tr>
<tr>
<td>• Minimally symptomatic</td>
<td>Topical hydrocortisone 1% or 2.5% cream and/or clindamycin 1% gel</td>
</tr>
<tr>
<td>• No impact on ADL(^*)</td>
<td></td>
</tr>
<tr>
<td>• No sign of superinfection</td>
<td>Reassess after 2 weeks; if reactions worsen or do not improve, proceed to next step</td>
</tr>
</tbody>
</table>

Rash grading and rash management are subjective and may vary according to the healthcare professional’s judgment, institutional guidelines, and patient’s 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.

Please see important safety information on back cover and enclosed full prescribing information.
**Rash severity grading**

<table>
<thead>
<tr>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Generalized</td>
<td>• Generalized</td>
</tr>
<tr>
<td>• Mild symptoms (eg, pruritus, tenderness)</td>
<td>• Severe symptoms (eg, pruritus, tenderness)</td>
</tr>
<tr>
<td>• Minimal impact on ADL*</td>
<td>• Significant impact on ADL*</td>
</tr>
<tr>
<td>• No sign of superinfection</td>
<td>• Potential for superinfection</td>
</tr>
</tbody>
</table>

**Intervention†**

**Moderate**
- 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

**Severe**
- 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

* 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.
Dosing & administration guidelines

Dose adjustment considerations

- Patients with severe skin reactions may require dose reduction or temporary interruption of therapy.¹
- To allow for dose reduction when appropriate, Tarceva is also available in 100-mg and 25-mg strengths.¹
- In clinical trials for both NSCLC and pancreatic cancer patients, the dose adjustment was held until symptom severity was Grade ≤1 (or mild), and then therapy resumed at a 50-mg lower dose.¹,²

Tarceva patients who smoke cigarettes should be advised to stop smoking. Cigarette smoking has been shown to reduce Tarceva exposure. The exact dose recommended for smokers is unknown; however, a cautious dose increase up to 300 mg may be considered while monitoring the patients’ safety. 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

- When dose reduction is necessary, Tarceva should be reduced by 50-mg decrements.¹
- Dose reduction is not appropriate if Interstitial Lung Disease (ILD), hepatic failure, or gastrointestinal perforation is diagnosed—Tarceva therapy should be discontinued. 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, and in patients with acute/worsening ocular disorders.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.

Please see important safety information on back cover and enclosed full prescribing information.
The most common adverse events for patients taking Tarceva for advanced NSCLC in clinical studies were rash and diarrhea, while the most common adverse events for patients taking Tarceva plus gemcitabine for advanced pancreatic cancer in clinical studies were fatigue, rash, nausea, anorexia, and diarrhea. The majority of these events were mild to moderate. Below are some possible approaches to managing these adverse events.

**Advanced NSCLC**

**Rash**
- See pages 6 and 7 for information on the management of Tarceva-related rash.
- Patients should be instructed to take Tarceva at least one hour before or two hours after the ingestion of food.
- Suggest patients use a thick, alcohol-free emollient cream on dry areas of the body.
- Suggest patients use a sunscreen of SPF 15 or higher, preferably containing zinc oxide or titanium dioxide.
- In the Tarceva pivotal clinical trial, patients who experienced NCI-CTC Grade 2 diarrhea were managed with loperamide.

**Diarrhea**
- Diarrhea is most likely to occur within the first week or two of Tarceva treatment.
- In the Tarceva pivotal clinical trial, patients who experienced NCI-CTC Grade 2 diarrhea were managed with loperamide.
- Rash and diarrhea each resulted in dose reductions in 1% of patients, and discontinuation in up to 1% of patients receiving Tarceva plus gemcitabine.
- Diarrhea: there have been reports of diarrhea being managed with loperamide.

**Advanced pancreatic cancer**

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

**Rash**
- As noted above.

**Nausea**
- Nausea may be managed with an antiemetic.

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

**Diarrhea**
- As noted above.

**Important safety information**

There have been infrequent reports of serious Intestinal Lymph Dismantle like events. When receiving Tarceva therapy, women should be advised against becoming pregnant or breastfeeding. Tarceva is pregnancy category D.
- There may be increased risks of bone marrow suppression, including neutropenia and anemia, in patients receiving Tarceva in combination with gemcitabine due to bone marrow depression associated with gemcitabine.
- When receiving Tarceva therapy, women should be advised against becoming pregnant or breastfeeding. Tarceva is pregnancy category D.
- Tarceva is a drug for people who have not responded to or have become resistant to previous chemotherapy. Tarceva is not recommended for the treatment of patients who have responded to or have become resistant to previous chemotherapy.
- There may be increased risks of bone marrow suppression, including neutropenia and anemia, in patients receiving Tarceva in combination with gemcitabine due to bone marrow depression associated with gemcitabine.
- Patients should be informed of the potential for severe skin reactions associated with Tarceva, including toxic epidermal necrolysis, which can result in death.
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- In the event of an acute onset of new or progressive, unexplained pulmonary symptoms such as dyspnea, cough and fever, Tarceva therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, Tarceva should be discontinued and appropriate treatment instituted as needed.
- Tarceva is generally well tolerated. There have been reports of diarrhea being managed with loperamide.
- The majority of adverse events were mild to moderate. Below are some possible approaches to managing these adverse events.

**Second-line advanced NSCLC**

Tarceva monotherapy is indicated for the treatment of patients with locally advanced or metastatic non small cell lung cancer (NSCLC) 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, and its use is not recommended in that setting.
- 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.
Patient rash assessment

Common Tarceva-related adverse events

The algorithm and general rash management considerations featured on pages 6 and 7 were developed by medical advisors at a company-sponsored advisory board meeting in collaboration with Genentech, Inc.  The recommendations were subsequently published.1 The medical advisors 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.

Advanced NSCLC

Rash

• See pages 6 and 7 for information on the management of Tarceva-related rash.
• Patients should be instructed to take Tarceva at least one hour before or two hours after the ingestion of food.1,2
• Suggest patients use a sunscreen of SPF 15 or higher, preferably containing zinc oxide or titanium dioxide.3,4
• Diarrhea
• Diarrhea is most likely to occur within the first week or two of Tarceva treatment.1
• In the Tarceva pivotal clinical trial, patients who experienced NCI-CTC Grade 2 diarrhea were managed with loperamide.1,2

Advanced pancreatic cancer

Fatigue
• Short rests throughout the day may help patients ward off fatigue.1

Rash
• As noted above.

Nausea
• Nausea may be managed with an antiepileptic.1

Anorexia
• Modifications in diet may help offset the loss of appetite.1

Diarrhea
• As noted above.

Important safety information

There have been infrequent reports of serious Interstitial Lung Disease (ILD)-like events, including fatalities, in patients receiving Tarceva for treatment of NSCLC, pancreatic cancer or other advanced solid tumors. In the event of an acute onset of new or progressive, unexplained pulmonary symptoms such as dyspnea, cough and fever, Tarceva therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, Tarceva should be discontinued and appropriate treatment instituted as needed.

Cases of hepatic failure, hepatorenal syndrome, acute renal failure (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 x ULN. Liver 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 was fatal. Interruption or discontinuation of Tarceva treatment should be considered if the patient develops severe bullous, blistering or exfoliative skin diseases.1,2

In the pancreatic cancer trial, other serious adverse reactions associated with Tarceva plus gemcitabine and which may have included fatalities, were mycocardial infarction/ ischemia, cerebrovascular accident and microangiopathic hemolytic anemia with thrombocytopenia.

Peritoneal perforation and ulceration have been reported during use of Tarceva. Interruption or discontinuation of Tarceva therapy if patients present with acute/worsening ocular disorders such as eye pain.

When receiving Tarceva therapy, women should be advised against becoming pregnant or breastfeeding. Tarceva is pregnancy category D.

The most common adverse reactions in patients with NSCLC receiving Tarceva monotherapy 150 mg were moderate rash and diarrhea. Severe rash and diarrhea (9% & 6% NCI-CTC Grades 3–4, respectively) were reported. Rash, nausea, fatigue and diarrhea each resulted in dose reductions (6% and 1%, respectively) and discontinuation in 1% of Tarceva-treated patients during the single-agent Phase III trial.

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.

Visit Tarceva.com for additional information and resources. Models are for illustrative purposes only.