Current Strategies in the Treatment of Advanced Non-small Cell Lung Cancer

a report by
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The field of lung cancer therapy remains dynamic. In the last several years, erlotinib (Tarceva, Genentech/OSI Pharmaceuticals) and pemetrexed (Alimta, Eli Lilly and Company) have gained approval for the treatment of lung cancer, and drugs such as bevacizumab have demonstrated success in combination with chemotherapy as first-line therapy against NSCLC. As more novel drugs and treatments continue to receive approval, strategies other than chemotherapy may be integrated into the frontline setting. Because previous clinical trials combining biologic therapies with chemotherapy have not been successful in improving survival, discoveries defining certain patient populations (e.g. those with specific biomarker abnormalities of the epidermal growth factor receptor (EGFR)) may allow earlier treatment with biologic compounds in selected patients.

In the past decade, several drugs have been identified with single-agent activity against NSCLC, showing partial response (PR) rates consistently in the range of 20–30%. These include docetaxel (Taxotere, Sanofi-Aventis), paclitaxel, gemcitabine (Gemzar, Eli Lilly), vinorelbine (Navelbine, GlaxoSmithKline), and irinotecan (Camptosar, Pfizer). As they have been identified, follow-up studies have been conducted with these newer drugs in combination with platinum compounds (cisplatin and/or carboplatin) demonstrating increased efficacy when these drugs are administered concurrently with another chemotherapeutic agent (doublet therapy).

Frontline Therapy

In most cases, phase III trials comparing numerous platinum-based doublets have failed to demonstrate superiority of one single combination regimen. Paclitaxel/cisplatin (PC) was compared to gemcitabine/cisplatin (GC), docetaxel/cisplatin (DC), paclitaxel/carboplatin (PCb) in the Eastern Cooperative Oncology Group (ECOG) E1594. This trial reported objective response rate (ORR) of 19%, median survival of 7.9 months, and one- and two-year survival rates of 33% and 11%, respectively, with no significant differences in the ORR and survival between PC and the other three regimens. In contrast, Rosell et al. published the results of a 618-patient trial of the combination of PC versus PCb; the combination of PC was associated with a significantly superior median survival (9.8 vs 8.2 months). Toxicities were low and comparable in the two arms. Moreover, the combination of vinorelbine/cisplatin (VC) was compared to PCb in the SWOG 9509 trial, and demonstrated similar response rates and median survival; less toxicity was noted in the PCb group, although there was no significant difference in quality of life (QOL).

The largest front-line trial reported to date in advanced lung cancer is the TAX 326 trial, which enrolled 1,218 patients with a good performance status; DC or docetaxel plus carboplatin (DCb) was compared with a control regimen of VC every four weeks. The mean age of the patients was 60 years, 75% were men, and approximately two-thirds had stage IV disease. Unlike the previous trials, TAX 326 demonstrated a survival benefit in one of the treatment arms. For DC versus VC, median survival was 11.3 months versus 10.1 months which reached significance ($P<0.05$); one-year survival was 46% versus 41%; and two-year survival was 21% versus 14%; all favoring DC. Global QOL, measured by the EuroQOL5D Scale, was better for the DC regimen ($p=0.016$). For DCb versus VC, median survival was 9.4 months versus 9.9 months; one-year survival was 38% versus 40%; and two-year survival was 18% versus 14%. The DCb arm showed global QOL benefits, measured by both the EuroQOL5D ($p=0.001$) and the Lung Cancer Symptom Scale ($p=0.016$). Performance status was better maintained in both docetaxel-containing arms, and weight loss of 10% or more was less frequent in these arms (7% vs 15%; $p<0.001$).

ECOG 4599 (phase II/III trial) recently reported on the addition of bevacizumab to PCb therapy in patients with advanced, metastatic, or recurrent non-squamous cell NSCLC. In this trial, 878 patients were randomized to receive either PC, or the same chemotherapy plus bevacizumab on day one every three weeks. After six cycles, chemotherapy was discontinued and patients in the experimental arm received single-agent bevacizumab. Patients excluded from E4599 were those at an increased risk of bleeding with bevacizumab as demonstrated by the phase II trial: patients with squamous histology, brain metastasis, or gross hemoptysis. Significant improvement

A therapeutic advance in second-line NSCLC

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Safety and effectiveness have not been studied in pediatric patients.

Indication

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.

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.

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

The most common side effects in patients with NSCLC receiving Tarceva monotherapy were mild to moderate rash and diarrhea. Severe rash and diarrhea (9% & 6% NCI-CTC Grades 3–4, respectively) each resulted in 1% of Tarceva-treated patients discontinuing the single-agent Phase III trial.

See accompanying brief summary of full prescribing information.

For further information, please call **1-877-TARCEVA (1-877-827-2382)** or visit our website at **www.tarceva.com**.

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TARCEVA® (erlotinib) TABLETS BRIEF SUMMARY

INDICATIONS AND USAGE Non-Small Cell Lung Cancer 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 3 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. **CONTRAINDICATIONS** None. **WARNINGS Pulmonary Toxicity** 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 randomized single-agent NSCLC study (see **CLINICAL STUDIES** section), the incidence of ILD-like events (0.8%) was the same in both the placebo and TARCEVA groups. In the pancreatic cancer study–in combination with gemcitabine–(see **CLINICAL STUDIES** section), the incidence of ILD-like events was 2.5% in the TARCEVA plus gemcitabine group vs. 0.4% in the placebo plus gemcitabine group. The overall incidence of ILD-like events in approximately 4900 TARCEVA-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) was approximately 0.7%. Reported diagnoses in patients suspected of having ILD-like events included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome and lung infiltration. Symptoms started from 5 days to more than 9 months (median 39 days) after initiating TARCEVA therapy. In the lung cancer trials most of the cases were associated with confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections. 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 (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION - Dose Modifications** sections). **Myocardial infarction/ischemia:** In the pancreatic carcinoma trial, six patients (incidence of 2.3%) in the TARCEVA/gemcitabine group developed myocardial infarction/ischemia. One of these patients died due to myocardial infarction. In comparison, 3 patients in the placebo/gemcitabine group developed myocardial infarction (incidence 1.2%) and one died due to myocardial infarction. **Cerebrovascular accident:** In the pancreatic carcinoma trial, six patients in the TARCEVA/gemcitabine group developed cerebrovascular accidents (incidence: 2.3%). One of these was hemorrhagic and was the only fatal event. In comparison, in the placebo/gemcitabine group there were no cerebrovascular accidents. **Microangiopathic Hemolytic Anemia with Thrombocytopenia:** In the pancreatic carcinoma trial, two patients in the TARCEVA/gemcitabine group developed microangiopathic hemolytic anemia with thrombocytopenia (incidence: 0.8%). Both patients received TARCEVA and gemcitabine concurrently. In comparison, in the placebo/gemcitabine group there were no cases of microangiopathic hemolytic anemia with thrombocytopenia. **Pregnancy Category D** Erlotinib has been shown to cause maternal toxicity with associated embryo/fetal lethality and abortion in rabbits when given at doses that result in plasma drug concentrations of approximately 3 times those in humans (AUCs at 150 mg daily dose). When given during the period of organogenesis to achieve plasma drug concentrations approximately equal to those in humans, based on AUC, there was no increased incidence of embryo/fetal lethality or abortion in rabbits or rats. However, female rats treated with 30 mg/m^2/day or 60 mg/m^2/day (0.3 or 0.7 times the clinical dose, on a mg/m^2 basis) of erlotinib prior to mating through the first week of pregnancy had an increase in early resorptions that resulted in a decrease in the number of live fetuses. No teratogenic effects were observed in rabbits or rats. There are no adequate and well-controlled studies in pregnant women using TARCEVA. Women of childbearing potential should be advised to avoid pregnancy while on TARCEVA. Adequate contraceptive methods should be used during therapy, and for at least 2 weeks after completing therapy. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the fetus. If TARCEVA is used during pregnancy, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy. **PRECAUTIONS Drug Interactions** Co-treatment with the potent CYP3A4 inhibitor ketoconazole increases erlotinib AUC by 2/3. Caution should be used when administering or taking TARCEVA with ketoconazole and other strong CYP3A4 inhibitors such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), and voriconazole (see **DOSAGE AND ADMINISTRATION - Dose Modifications** section). Pre-treatment with the CYP3A4 inducer rifampicin decreased erlotinib AUC by about 2/3. Alternate treatments lacking CYP3A4 inducing activity should be considered. If an alternative treatment is unavailable, a TARCEVA dose greater than 150 mg should be considered for NSCLC patients, and greater than 100 mg considered for pancreatic cancer patients. If the TARCEVA dose is adjusted upward, the dose will need to be reduced upon discontinuation of rifampicin or other inducers. Other CYP3A4 inducers include, but are not limited to, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital and St. John's Wort (see **DOSAGE AND ADMINISTRATION - Dose Modifications** section). **Hepatotoxicity** Asymptomatic increases in liver transaminases have been observed in TARCEVA treated patients; therefore, periodic liver function testing (transaminases, bilirubin, and alkaline phosphatase) should be considered. Dose reduction or interruption of TARCEVA should be considered if changes in liver function are severe (see **ADVERSE REACTIONS** section). **Patients with Hepatic Impairment** *In vitro* and *in vivo* evidence suggest that erlotinib is cleared primarily by the liver. Therefore, erlotinib exposure may be increased in patients with hepatic dysfunction (see **CLINICAL PHARMACOLOGY - Special Populations - Patients with Hepatic Impairment** and **DOSAGE AND ADMINISTRATION - Dose Modification** sections). **Elevated International Normalized Ratio and Potential Bleeding** International Normalized Ratio (INR) elevations and infrequent reports of bleeding events including gastrointestinal and non-gastrointestinal bleedings 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 (see **ADVERSE REACTIONS** section). **Carcinogenesis, Mutagenesis, Impairment of Fertility** Erlotinib has not been tested for carcinogenicity. Erlotinib has been tested for genotoxicity in a series of *in vitro* assays (bacterial mutation, human lymphocyte chromosome aberration, and mammalian cell mutation) and an *in vivo* mouse bone marrow micronucleus test and did not cause genetic damage. Erlotinib did not impair fertility in either male or female rats. **Pregnancy Pregnancy Category D** (see **WARNINGS** and **PRECAUTIONS - Information for Patients** sections). **Nursing Mothers** It is not known whether erlotinib is excreted in human milk. Because many drugs are excreted in human milk and because the effects of TARCEVA on infants have not been studied, women should be advised against breast-feeding while receiving TARCEVA therapy. **Pediatric Use** The safety and effectiveness of TARCEVA in pediatric patients have not been studied. **Geriatric Use** Of the total number of patients participating in the randomized NSCLC trial, 62% were less than 65 years of age, and 38% of patients were aged 65 years or older. The survival benefit was maintained across both age groups (see **CLINICAL STUDIES** section). In the pancreatic cancer study, 53% of patients were younger than 65 years of age and 47% were 65 years of age or older. No meaningful differences in safety or pharmacokinetics were observed between younger and older patients in either study. Therefore, no dosage adjustments are recommended in elderly patients. **Information for Patients** If the following signs or symptoms occur, patients should seek medical advice promptly (see **WARNINGS, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION - Dose Modification** sections). • Severe or persistent diarrhea, nausea, anorexia, or vomiting • Onset or worsening of unexplained shortness of breath or cough • Eye irritation. Women of childbearing potential should be advised to avoid becoming pregnant while taking TARCEVA (see **WARNINGS - Pregnancy Category D** section). **ADVERSE REACTIONS** Safety evaluation of TARCEVA is based on 856 cancer patients who received TARCEVA as monotherapy, 308 patients who received TARCEVA 100 or 150 mg plus gemcitabine, and 1228 patients who received TARCEVA concurrently with other chemotherapies. There have been reports of serious events, including fatalities, in patients receiving TARCEVA for treatment of NSCLC, pancreatic cancer or other advanced solid tumors (see **WARNINGS,** and **DOSAGE AND ADMINISTRATION - Dose Modifications** sections). **Non-Small Cell Lung Cancer** Adverse events, regardless of causality, that occurred in at least 10% of patients treated with single-agent TARCEVA at 150 mg and at least 3% more often than in the placebo group in the randomized trial of patients with NSCLC are summarized by NCI-CTC (version 2.0) Grade in Table 5. The most common adverse reactions in patients receiving single-agent TARCEVA 150 mg were rash and diarrhea. Grade 3/4 rash and diarrhea occurred in 9% and 6%, respectively, in TARCEVA-treated patients. Rash and diarrhea each resulted in study discontinuation in 1% of TARCEVA-treated patients. Six percent and 1% of patients needed dose reduction for rash and diarrhea, respectively. The median time to onset of rash was 8 days, and the median time to onset of diarrhea was 12 days. **Table 5: Adverse Events Occurring in ≥10% of Single-Agent TARCEVA-treated Non-Small Cell Lung Cancer Patients (2:1 Randomization of TARCEVA to Placebo)**

	TARCEVA 150 mg 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
Anorexia	52	8	1	38	5	<1
Fatigue	52	14	4	45	16	4
Dyspnea	41	17	11	35	15	11
Cough	33	4	0	29	2	0
Nausea	33	3	0	24	2	0
Infection	24	4	0	15	2	0
Vomiting	23	2	<1	19	2	0
Stomatitis	17	<1	0	3	0	0
Pruritus	13	<1	0	5	0	0
Dry skin	12	0	0	4	0	0
Conjunctivitis	12	<1	0	2	<1	0
Keratoconjunctivitis sicca	12	0	0	3	0	0
Abdominal pain	11	2	<1	7	1	<1

Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) were observed in patients receiving single-agent TARCEVA 150 mg. These elevations were mainly transient or associated with liver metastases. Grade 2 (>2.5–5.0 x ULN) ALT elevations occurred in 4% and <1% of TARCEVA and placebo treated patients, respectively. Grade 3 (>5.0–20.0 x ULN) elevations were not observed in TARCEVA-treated patients. Dose reduction or interruption of TARCEVA should be considered if changes in liver function are severe (see **DOSAGE AND ADMINISTRATION - Dose Modification** section). **Pancreatic Cancer** Adverse events, regardless of causality, that occurred in at least 10% of patients treated with TARCEVA 100 mg plus gemcitabine in the randomized trial of patients with pancreatic cancer are summarized by NCI-CTC (version 2.0) Grade in Table 6. The most common adverse reactions in pancreatic cancer patients receiving TARCEVA 100 mg plus gemcitabine were fatigue, rash, nausea, anorexia and diarrhea. In the TARCEVA plus gemcitabine arm, Grade 3/4 rash and diarrhea were each reported in 5% of TARCEVA plus gemcitabine-treated patients. The median time to onset of rash and diarrhea was 10 days and 15 days, respectively. Rash and diarrhea each resulted in dose reductions in 2% of patients, and resulted in study discontinuation in up to 1% of patients receiving TARCEVA plus gemcitabine. The 150 mg cohort was associated with a higher rate of certain class-specific adverse reactions including rash and required more frequent dose reduction or interruption. **Table 6: Adverse Events Occurring in ≥10% of TARCEVA-treated Pancreatic Cancer Patients: 100 mg cohort**

	TARCEVA + Gemcitabine 1000 mg/m^2 IV N = 259			Placebo + Gemcitabine 1000 mg/m^2 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
Abdominal pain	46	9	<1	45	12	<1
Vomiting	42	7	<1	41	4	<1
Weight decreased	39	2	0	29	<1	0
Infection*	39	13	3	30	9	2
Edema	37	3	<1	36	2	<1
Pyrexia	36	3	0	30	4	0
Constipation	31	3	1	34	5	1
Bone pain	25	4	<1	23	2	0
Dyspnea	24	5	<1	23	5	0
Stomatitis	22	<1	0	12	0	0
Myalgia	21	1	0	20	<1	0
Depression	19	2	0	14	<1	0
Dyspepsia	17	<1	0	13	<1	0
Cough	16	0	0	11	0	0
Dizziness	15	<1	0	13	0	<1
Headache	15	<1	0	10	0	0
Insomnia	15	<1	0	16	<1	0
Alopecia	14	0	0	11	0	0
Anxiety	13	1	0	11	<1	0
Neuropathy	13	1	<1	10	<1	0
Flatulence	13	0	0	9	<1	0
Rigors	12	0	0	9	0	0

*Includes all MedDRA preferred terms in the Infections and Infestations System Organ Class

In the pancreatic carcinoma trial, 10 patients in the TARCEVA/gemcitabine group developed deep venous thrombosis (incidence: 3.9%). In comparison, 3 patients in the placebo/gemcitabine group developed deep venous thrombosis (incidence 1.2%). The overall incidence of grade 3 or 4 thrombotic events, including deep venous thrombosis, was similar in the two treatment arms: 11% for TARCEVA plus gemcitabine and 9% for placebo plus gemcitabine. No differences in Grade 3 or Grade 4 hematologic laboratory toxicities were detected between the TARCEVA plus gemcitabine group compared to the placebo plus gemcitabine group. Severe adverse events (≥grade 3 NCI-CTC) in the TARCEVA plus gemcitabine group with incidences < 5% included syncope, arrhythmias, ileus, pancreatitis, hemolytic anemia including microangiopathic hemolytic anemia with thrombocytopenia, myocardial infarction/ischemia, cerebrovascular accidents including cerebral hemorrhage, and renal insufficiency (see **WARNINGS** section). Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) have been observed following the administration of TARCEVA plus gemcitabine in patients with pancreatic cancer. Table 7 displays the most severe NCI-CTC grade of liver function abnormalities that developed. Dose reduction or interruption of TARCEVA should be considered if changes in liver function are severe (see **DOSAGE AND ADMINISTRATION - Dose Modification** section). **Table 7: Liver Function Test Abnormalities (most severe NCI-CTC grade) in Pancreatic Cancer Patients: 100 mg Cohort**

	TARCEVA + Gemcitabine 1000 mg/m^2 IV N = 259			Placebo + Gemcitabine 1000 mg/m^2 IV N = 256		
NCI CTC Grade	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**
Bilirubin	17%	10%	<1%	11%	10%	3%
ALT	31%	13%	<1%	22%	9%	0%
AST	24%	10%	<1%	19%	9%	0%

NSCLC and Pancreatic Cancer Indications During the NSCLC and the combination pancreatic cancer trials, infrequent cases of gastrointestinal bleeding have been reported, some associated with concomitant warfarin or NSAID administration (see **PRECAUTIONS - Elevated International Normalized Ratio and Potential Bleeding** section). These adverse events were reported as peptic ulcer bleeding (gastritis, gastroduodenal ulcers), hematemesis, hematochezia, melena and hemorrhage from possible colitis (see **PRECAUTIONS** section). Cases of Grade 1 epistaxis were also reported in both the single-agent NSCLC and the pancreatic cancer clinical trials. NCI-CTC Grade 3 conjunctivitis and keratitis have been reported infrequently in patients receiving TARCEVA therapy in the NSCLC and pancreatic cancer clinical trials. Corneal ulcerations may also occur (see **PRECAUTIONS - Information for Patients** section). In general, no notable differences in the safety of TARCEVA monotherapy or in combination with gemcitabine could be discerned between females or males and between patients younger or older than the age of 65 years. The safety of TARCEVA appears similar in Caucasian and Asian patients (see **PRECAUTIONS - Geriatric Use** section). **OVERDOSAGE** Single oral doses of TARCEVA up to 1,000 mg in healthy subjects and up to 1,600 mg in cancer patients have been tolerated. Repeated twice-daily doses of 200 mg single-agent TARCEVA in healthy subjects were poorly tolerated after only a few days of dosing. Based on the data from these studies, an unacceptable incidence of severe adverse events, such as diarrhea, rash, and liver transaminase elevation, may occur above the recommended dose (see **DOSAGE AND ADMINISTRATION** section). In case of suspected overdose, TARCEVA should be withheld and symptomatic treatment instituted. **DOSAGE AND ADMINISTRATION Non-Small Cell Lung Cancer** The recommended daily dose of TARCEVA is 150 mg taken at least one hour before or two hours after the ingestion of food. Treatment should continue until disease progression or unacceptable toxicity occurs. There is no evidence that treatment beyond progression is beneficial. **Pancreatic Cancer** The recommended daily dose of TARCEVA is 100 mg taken at least one hour before or two hours after the ingestion of food, in combination with gemcitabine (see the gemcitabine package insert). Treatment should continue until disease progression or unacceptable toxicity occurs. **Dose Modifications** 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 ILD is diagnosed, TARCEVA should be discontinued and appropriate treatment instituted as necessary (see **WARNINGS - Pulmonary Toxicity** section). 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. When dose reduction is necessary, the TARCEVA dose should be reduced in 50 mg decrements. In patients who are being concomitantly treated with a strong CYP3A4 inhibitor such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), or voriconazole, a dose reduction should be considered should severe adverse reactions occur. Pre-treatment with the CYP3A4 inducer rifampicin decreased erlotinib AUC by about 2/3. Alternate treatments lacking CYP3A4 inducing activity should be considered. If an alternative treatment is unavailable, a TARCEVA dose greater than 150 mg should be considered. If the TARCEVA dose is adjusted upward, the dose will need to be reduced upon discontinuation of rifampicin or other inducers. Other CYP3A4 inducers include, but are not limited to rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital and St. John's Wort. These too should be avoided if possible (see **PRECAUTIONS - Drug Interactions** section). Erlotinib is eliminated by hepatic metabolism and biliary excretion. Therefore, caution should be used when administering TARCEVA to patients with hepatic impairment. Dose reduction or interruption of TARCEVA should be considered should severe adverse reactions occur (see **CLINICAL PHARMACOLOGY - Special Populations - Patients With Hepatic Impairment, PRECAUTIONS - Patients With Hepatic Impairment**, and **ADVERSE REACTIONS** sections). **HOW SUPPLIED** The 25 mg, 100 mg and 150 mg strengths are supplied as white film-coated tablets for daily oral administration. TARCEVA® (erlotinib) Tablets, 25 mg: Round, biconvex face and straight sides, white film-coated, printed in orange with a "T" and "25" on one side and plain on the other side. Supplied in bottles of 30 tablets (NDC 50242-062-01). TARCEVA® (erlotinib) Tablets, 100 mg: Round, biconvex face and straight sides, white film-coated, printed in gray with "T" and "100" on one side and plain on the other side. Supplied in bottles of 30 tablets (NDC 50242-063-01). TARCEVA® (erlotinib) Tablets, 150 mg: Round, biconvex face and straight sides, white film-coated, printed in maroon with "T" and "150" on one side and plain on the other side. Supplied in bottles of 30 tablets (NDC 50242-064-01). **STORAGE** Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F). See USP Controlled Room Temperature.

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in median survival (12.5 months vs 10.2 months), ORR (27% vs 10%), and time-to-tumor progression (TTP) (6.4 months vs 4.5 months) were observed, all favoring the bevacizumab arm. As expected, a higher incidence of bleeding was associated with bevacizumab administration (4.5% vs 0.7%).

Salvage Therapy

Treatment of NSCLC has changed dramatically over the past several years as more drugs have been introduced for treating patients who have failed priory chemotherapy. In a phase III study comparing docetaxel to best supportive care, TTP was significantly longer for the patients who received docetaxel (10.6 vs 6.7 weeks, respectively; $p<.001$), as was median (7.0 vs 4.6 months) and one-year survival (37% vs 11%). In the TAX 320 trial, two different doses of docetaxel (100mg/m^2 and 75mg/m^2) were compared against vinorelbine or ifosfamide. Although response rates to docetaxel were low (11% for the high dose and 7% for the low dose), they were significantly higher than the vinorelbine or ifosfamide arms (1%). Patients receiving either docetaxel regimen demonstrated a QOL benefit. Furthermore, the one-year survival was significantly greater with docetaxel 75mg/m^2 compared with the ifosfamide or vinorelbine treatment (32% vs 19%; $p=.025$).

The antifolate agent, pemetrexed, has also been approved for salvage therapy in NSCLC, after previously being approved for mesothelioma with cisplatin. In a 571-patient phase III study comparing pemetrexed to docetaxel, outcomes did not reach significance between the two groups, with ORR approximately 9%, median progression-free survival (PFS) of 2.9 months for each arm, median survival time of 8.3 versus 7.9 months for pemetrexed and docetaxel, respectively, and one-year survival rate of 29.7% for each arm. However, pemetrexed was associated with significantly fewer side effects.

In view of poor outcomes with cytotoxic chemotherapy in salvage treatment, EGFR tyrosine-kinase inhibitors (TKIs) were investigated in second-line therapy for NSCLC. Initial phase II studies with gefitinib appeared promising; however, further studies failed to show a significant survival difference compared with placebo and best supportive care. In contrast, erlotinib has shown efficacy in second-line NSCLC therapy similar to that noted with cytotoxic agents. Shepherd et al. conducted a 731-patient randomized placebo controlled trial of erlotinib versus placebo in second or third line therapy. Significant differences in outcomes, including response rate (8.9% vs <1%), PFS (2.2 months vs 1.8 months), overall survival (6.7 months vs 4.7 months) and QOL, were noted, all favoring the erlotinib arm; only 5% of patients discontinued erlotinib because of toxic effects.

Docetaxel, pemetrexed, and erlotinib are the three currently approved single-agents in the salvage therapy of NSCLC.

Molecular Targeted Therapies

Because of the discouraging survival statistics associated with NSCLC, additional approaches to treatment have been pursued diligently, including the use of targeted agents alone or in combination with chemotherapy.

Epidermal Growth Factor Receptor

EGFR is a tansmembrane glycoprotein receptor composed of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain with a TK region. Altered or increased expression of EGFR has been observed in 60–80% of patients with lung cancer and has been linked to disease progression, poor survival, poor response to therapy, development of resistance to cytotoxic agents, advanced tumor stage, and increased risk for metastasis. Overexpression of EGFR is most commonly found in squamous cell (84%), followed by large cell (68%) and adenocarcinoma (65%). The inhibition of EGFR can therefore be accomplished upstream by blocking the ligand-binding domain with monoclonal antibodies (i.e. cetuximab) or downstream by interfering with signal transduction via TK by using small molecule TKIs (i.e. erlotinib and gefitinib).

Erlotinib

Erlotinib, an orally active quinazoline, is a potent selective inhibitor of EGFR TK. The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) conducted the BR.21 trial which evaluated erlotinib in the setting of second- or third-line therapy for advanced NSCLC. This study was the first to demonstrate a statistically significant survival benefit associated with the use of a biologic agent. In BR.21, Shepherd et al. randomized 731 patients with previously treated advanced NSCLC to receive erlotinib 150mg per day or placebo. The ORR and overall survival with erlotinib were 8.9% and 6.7 months, respectively, compared with <1% and 4.7 months for the patients receiving placebo ($p=0.001$). PFS was 2.2 months in the erlotinib group, compared with 1.8 months in the placebo group ($p<0.001$), and QOL measurements also significantly favored the erlotinib group. In addition, all subgroups benefited from therapy with erlotinib, including men, women, and those with squamous as well as adenocarcinoma. On the basis of this study, erlotinib was approved by the US Food and Drug Administration (FDA) in November 2004 for the treatment of locally advanced or metastatic NSCLC that has failed to respond to at least one prior chemotherapy regimen. In view of its activity in the salvage setting, a

large adjuvant study with erlotinib based on tumor profile is planned to further evaluate its role in the treatment of NSCLC.

Gefitinib

Gefitinib (Iressa, AstraZeneca), which gained accelerated approval in May 2003 for the treatment of advanced NSCLC, is also a selective EGFR TKI. Initial studies using this agent were very promising. Recently, ISEL (Iressa Survival Evaluation in Lung Cancer), a placebo-controlled, randomized phase III trial of more than 1,600 patients, reported no statistically significant difference in survival between patients treated with gefitinib and those given placebo. Gefitinib is therefore no longer recommended in the treatment of NSCLC.

Cetuximab

Cetuximab (Erbitux, ImClone Systems/Bristol-Myers Squibb), a promising monoclonal antibody targeting the EGFR, has been approved for use in colorectal cancer and recently in head/neck squamous cell cancer.

Studies examining cetuximab as a treatment for patients with NSCLC are on-going. In first-line treatment of patients with metastatic disease, the addition of cetuximab to PC, gemcitabine/carboplatin (GCb), VC are currently under way. In the setting of second-line treatment of NSCLC, a recent study reported on the use of docetaxel plus cetuximab in patients with EGFR-positive tumors. The results were encouraging, with a response rate of 25–30% in this chemotherapy-refractory patient population. A phase III trial is on-going in this patient population with docetaxel or pemetrexed +/- cetuximab.

VEGF Signaling Pathway

Angiogenesis plays an important role in the growth and metastasis of solid tumors. vascular endothelial growth factor (VEGF), its isoforms, and its receptor (VEGFR) are important in regulating angiogenesis. Multiple strategies have been developed to target this pathway.

One approach to the modulation of VEGF-mediated angiogenesis is to use antibodies targeted against the VEGF protein itself, or to its receptor. Encouraging results have been reported with the addition of bevacizumab to PCb (ECOG 4599) in patients with advanced, metastatic, or recurrent non-squamous cell NSCLC. A phase II randomized second-line trial of chemotherapy + placebo, chemotherapy with bevacizumab, and erlotinib with bevacizumab was reported at American Society of Clinical Oncology (ASCO) this year. The results demonstrated improved PFS (primary endpoint) in favor of both bevacizumab arms and a better response rate with the bevacizumab and erlotinib combination. This combination of erlotinib and bevacizumab is being studied in a large phase III randomized study in the second-line setting.

ZD6474 (AstraZeneca) is an oral agent with dual kinase inhibitor activity which targets both VEGFR-2 and EGFR TKs. ZD6474 has shown activity in NSCLC and other solid tumor types. This small molecule inhibitor therefore affects two distinct processes involved in tumor growth and survival: cell proliferation and angiogenesis. Phase I studies with ZD6474 have been completed and demonstrated good tolerability at an oral dose ≤300mg, and manageable side effects. Although phase II studies with ZD 6474 are currently on-going, preliminary data from two studies appear promising.

Other compounds are actively being studied in NSCLC. These include BAY 43-9006 (Sorafenib, Bayer), a potent inhibitor of both Raf kinase signaling pathway (involved in cell proliferation), as well as VEGFR2 and platelet derived growth factor receptor (PDGFR)-β (involved in angiogenesis). BAY 43-9006 has demonstrated promising anti-tumor activity in a number of tumor types including renal cell carcinoma (RCC), sarcoma, melanoma, and pancreatic, thyroid, and colorectal cancers. Sunitinib (Sutent) is an oral multi-kinase inhibitor (VEGFR, PDGFR-α, PDGFR-β, RET, KIT, FLT-3) and is approved for use in renal cell cancer and imatinib-refractory GIST. Sunitinib has been studied in NSCLC with response rates of about 10%. Further studies are planned in combination.

Conclusion

The treatment of advanced lung cancer remains an exciting area that reflects a sobering challenge. Cytotoxic chemotherapy doublets have modestly improved survival, and research is now emphasizing QOL issues. Agents targeting VEGF and EGFR have become critical weapons in the treatment of NSCLC. Bevacizumab and erlotinib are the first biologic agents to demonstrate a survival advantage when added to standard chemotherapy. Other strategies are being evaluated including earlier detection, predictive markers, and chemoprevention. As research on genomic and proteomic techniques continues, therapy tailored to specific tumors may offer an opportunity for improved efficacy and disease control with the use of both cytotoxic and biologic compounds. ■

A version of this article containing references can be found in the Reference Section on the website supporting this briefing (www.touchoncology.com).