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Highlights in NSCLC From the American Society of Clinical Oncology Meeting

June 3–7, 2011
Chicago, Illinois

Special Reporting on:

- PARAMOUNT: Pemetrexed Plus Best Supportive Care
- Identification of Driver Mutations in Lung Adenocarcinoma
- Interim Results of the EURTAC Trial
- Erlotinib/Bevacizumab Versus Cisplatin/Gemcitabine Plus Bevacizumab in First-Line Treatment
- Impact of Crizotinib on Survival in ALK-Positive NSCLC
- Ganetespib as Monotherapy in Advanced NSCLC

PLUS Meeting Abstract Summaries

With Expert Commentary by:

Mark A. Socinski, MD
Professor of Medicine
Multidisciplinary Thoracic Oncology Program
Lineberger Comprehensive Cancer Center
University of North Carolina
Chapel Hill, North Carolina

After first-line treatment in mNSCLC—

Slow disease progression with Tarceva

NSCLC maintenance therapy indication

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.

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.

References: **1.** Mok TS, Ramalingam SS. Maintenance therapy in nonsmall-cell lung cancer: a new treatment paradigm. *Cancer*. 2009;115(22):5143-5154. **2.** 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. **3.** 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. **4.** Tarceva [package insert]. Melville, NY: OSI Pharmaceuticals Inc; 2010. **5.** 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. **6.** 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. **7.** Stinchcombe TE, Socinski MA. Considerations for second-line therapy of non-small cell lung cancer. *Oncologist*. 2008;13(suppl 1):28-36. **8.** 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. **9.** Stang A, Pohlabeln H, Müller KM, Jahn I, Giersiepen K, Jöckel K-H. Diagnostic agreement in the histopathological evaluation of lung cancer tissue in a population-based case-control study. *Lung Cancer*. 2006;52(1):29-36.

Please see accompanying brief summary of full prescribing information.

Preserve response to first-line treatment

What is maintenance therapy?

- Maintenance therapy is treatment with a different agent that begins immediately after first-line chemotherapy in patients without disease progression.[1]

Why use maintenance therapy?

- **Maintenance ensures patients receive active therapy after first-line treatment, which may prolong overall survival.**[2-4]
  - Rapid progression, declining performance status, and increased symptom burden may render patients unsuitable to receive further treatment.[5,6]
  - 31% of patients in recent maintenance clinical trials did not receive second-line treatment, in part due to complications associated with disease progression.[2,3,6-8]
  - Maintenance therapy may help increase post–first-line treatment rates.[2]
  - Two phase III maintenance studies have demonstrated a survival improvement.[3,4]

Which NSCLC patients should be treated with maintenance therapy?

- Patients who achieved a response after 4 cycles of chemotherapy are candidates for maintenance therapy.[1,4]

What do I need to consider when choosing a maintenance therapy?

- An agent that is indicated for both squamous and nonsquamous NSCLC[9]
- Patient preference for oral or IV therapy
- Benefits and risks of treatment

Why should I use Tarceva as maintenance therapy in NSCLC?

- **Tarceva is approved in the maintenance setting after first-line chemotherapy for a broad (ITT) patient population, irrespective of histology or biomarker status.**[4]
  - Tarceva monotherapy is indicated for the maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.[4]
  - 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.[4]
- **In the pivotal SATURN trial,* Tarceva demonstrated a significant benefit in OS and PFS in a broad (ITT) patient population.**[4]
  - 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)[4]
    - 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)[4]
- **Tarceva is the only FDA-approved, oral, noncytotoxic therapy for the treatment of NSCLC; the most common adverse reactions associated with Tarceva are generally manageable.**[4]
  - Serious adverse reactions have been associated with Tarceva therapy.[4]
    - Warnings and precautions associated with Tarceva 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.[4]
  - 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%).[4]

Important safety information

- There have been reports of serious Interstitial Lung Disease (ILD)-like events, including fatalities, in patients receiving Tarceva.
- Cases of hepatic failure, hepatorenal syndrome, acute renal failure (all including fatalities), and renal insufficiency have been reported during use of Tarceva.
- Gastrointestinal perforation (including fatalities) has been reported in patients receiving Tarceva.
- 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.
- Corneal perforation and ulceration have been reported during use of Tarceva.
- International Normalized Ratio (INR) elevation and infrequent reports of bleeding events, including gastrointestinal and non-gastrointestinal bleeding, have been reported in clinical studies.
- 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.

For more information regarding maintenance therapy, visit **Tarceva.com**.

* SATURN was an international, placebo-controlled, randomized, double-blind phase III study that included 889 patients with nonprogressive disease following 4 cycles of a first-line platinum-based doublet.[4]

Tarceva® erlotinib tablets

Genentech | (OSI) oncology

Proven to prolong survival

TARCEVA® (erlotinib) TABLETS BRIEF SUMMARY Please see the Tarceva package insert for full prescribing information. INDICATIONS AND USAGE 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 whose disease has not progressed after four cycles of platinum-based first-line chemotherapy *[see Clinical Studies (14.1)]*. 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 *[see Clinical Studies (14.2)]*. 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 *[see Clinical Studies (14.3)]*. **Pancreatic Cancer** TARCEVA in combination with gemcitabine is indicated for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer *[see Clinical Studies (14.4)]*. **CONTRAINDICATIONS** None **WARNINGS AND PRECAUTIONS Pulmonary Toxicity** 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. In the randomized single-agent NSCLC-studies *[see Clinical Studies (14.1, 14.2)]*, 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 and 3rd line study. In the pancreatic cancer study – in combination with gemcitabine – *[see Clinical Studies (14.4)]*, 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 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, 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 Dosage and Administration (2.3)]*. **Renal Failure** 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 *[see Adverse Reactions (6.1) and Dosage and Administration (2.3)]*. **Hepatotoxicity** 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 *[see Adverse Reactions (6.1, 6.2) and Dosage and Administration (2.3)]*. **Patients with Hepatic Impairment** In a pharmacokinetic study in patients with moderate hepatic impairment (Child-Pugh B) associated with significant liver tumor burden, 10 out of 15 patients died on treatment or within 30 days of the last TARCEVA dose. One patient died from hepatorenal syndrome, 1 patient died from rapidly progressing liver failure and the remaining 8 patients died from progressive disease. Six out of the 10 patients who died had baseline total bilirubin > 3 x ULN suggesting severe hepatic impairment. 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 *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.3)]*. **Gastrointestinal Perforation** 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. *[see Adverse Reactions (6.1, 6.2)]*. Permanently discontinue TARCEVA in patients who develop gastrointestinal perforation. **Bullous and Exfoliative Skin Disorders** 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 *[see Adverse Reactions (6.1, 6.2)]*. Interrupt or discontinue TARCEVA treatment if the patient develops severe bullous, blistering or exfoliating conditions. **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. **Ocular Disorders** 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 *[see Adverse Reactions (6.1)]*. Interrupt or discontinue TARCEVA therapy if patients present with acute/worsening ocular disorders such as eye pain. **Elevated International Normalized Ratio and Potential Bleeding** International Normalized Ratio (INR) elevations 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 *[see Adverse Reactions (6.1)]*. **Use in Pregnancy** TARCEVA can cause fetal harm when administered to a pregnant woman. Erlotinib administered to rabbits during organogenesis at doses that result in plasma drug concentrations of approximately 3 times those in humans at the recommended dose of 150 mg daily, was associated with embryofetal lethality and abortion. When erlotinib was administered to female rats prior to mating and through the first week of pregnancy, at doses 0.3 or 0.7 times the clinical dose of 150 mg, on a mg/m² basis, there was an increase in early resorptions that resulted in a decrease in the number of live fetuses *[see Use in Specific Populations (8.1)]*. 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. If TARCEVA is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Pregnancy Category D. **ADVERSE REACTIONS Clinical Trial Experience Non-Small Cell Lung Cancer Maintenance Study** Adverse reactions, regardless of causality, that occurred in at least 3% of patients treated with single-agent TARCEVA at 150 mg and at least 3% more often than in the placebo group in the randomized maintenance trial are summarized by NCI-CTC (version 3.0) Grade in Table 1. 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 6.0% and 1.8%, respectively, in TARCEVA-treated patients. Rash and diarrhea resulted in study discontinuation in 1.2% and 0.5% of TARCEVA-treated patients, respectively. Dose reduction or interruption for rash and diarrhea was needed in 5.1% and 2.8% of patients, respectively. In TARCEVA-treated patients who developed rash, the onset was within two weeks in 66% and within one month in 81%. **Table 1: NSCLC Maintenance Study: 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.**

	TARCEVA N = 433			PLACEBO N = 445		
NCI-CTC Grade	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
MedDRA Preferred Term	**%**	**%**	**%**	**%**	**%**	**%**
Rash	49.2	6.0	0	5.8	0	0
Diarrhea	20.3	1.8	0	4.5	0	0
Fatigue	9.0	1.8	0	5.8	1.1	0
Anorexia	9.2	<1	0	4.9	<1	0
Pruritus	7.4	<1	0	2.7	0	0
Acne	6.2	<1	0	0	0	0
Dermatitis Acneiform	4.6	<1	0	1.1	0	0
Dry Skin	4.4	0	0	<1	0	0
Weight Decreased	3.9	<1	0	<1	0	0
Paronychia	3.9	<1	0	0	0	0

Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) were observed in patients receiving single-agent TARCEVA 150 mg in the Maintenance study. Grade 2 (>2.5 – 5.0 x ULN) ALT elevations occurred in 2% and 1%, and Grade 3 (>5.0 – 20.0 x ULN) ALT elevations were observed in 1% and 0% of TARCEVA and placebo treated patients, respectively. The TARCEVA treatment group had Grade 2 (>1.5-3.0 x ULN) bilirubin elevations in 4% and Grade 3 (>3.0-10.0 x ULN) in <1% compared with <1% for both Grades 2 and 3 in the placebo group. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe *[see Dosage and Administration (2.3)]*. **Second/Third Line Study** Adverse reactions, 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 2. The most common adverse reactions in this patient population 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 2: NSCLC 2nd/3rd Line Study: 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.**

	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. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe. *[see Dosage and Administration (2.3)]*. **Pancreatic Cancer** Adverse reactions, 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 3. 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 3: Adverse Reactions Occurring in ≥ 10% of TARCEVA-treated Pancreatic Cancer Patients: 100 mg cohort**

	TARCEVA + Gemcitabine 1000 mg/m² IV N = 259			Placebo + Gemcitabine 1000 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
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 reactions (≥ 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 and Precautions (5)]*. 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 4 displays the most severe NCI-CTC grade of liver function abnormalities that developed. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe *[see Dosage and Administration (2.3)]*.

Table 4: Liver Function Test Abnormalities (most severe NCI-CTC grade) in Pancreatic Cancer Patients: 100 mg Cohort

	TARCEVA + Gemcitabine 1000 mg/m² IV N = 259			Placebo + Gemcitabine 1000 mg/m² 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 Indications: Low Frequency Adverse Reactions Gastrointestinal Disorders Gastrointestinal perforations have been reported *[see Warnings and Precautions (5.5)]*. 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 Warnings and Precautions (5.11)]*. These adverse reactions were reported as peptic ulcer bleeding (gastritis, gastroduodenal ulcers), hematemesis, hematochezia, melena and hemorrhage from possible colitis. **Renal Disorders** Cases of acute renal failure or renal insufficiency, including fatalities, with or without hypokalemia have been reported *[see Warnings and Precautions (5.2)]*. **Hepatic Disorders** Hepatic failure has been reported in patients treated with single-agent TARCEVA or TARCEVA combined with chemotherapy *[see Warnings and Precautions (5.3)]*. **Ocular Disorders** Corneal ulcerations or perforations have been reported in patients receiving TARCEVA treatment. Abnormal eyelash growth including in-growing eyelashes, excessive growth and thickening of the eyelashes have been reported *[see Warnings and Precautions (5.10)]* and are risk factors for corneal ulceration/perforation. NCI-CTC Grade 3 conjunctivitis and keratitis have been reported infrequently in patients receiving TARCEVA therapy in the NSCLC and pancreatic cancer clinical trials. *[see Patient Counseling Information (17)]*. **Skin, Hair, and Nail Disorders** Bullous, blistering and exfoliative skin conditions have been reported including cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis *[see Warnings and Precautions (5.6)]*. In patients who develop skin rash, the appearance of the rash is typically erythematous and maculopapular and it may resemble acne with follicular pustules, but is histopathologically different. This skin reaction commonly occurs on the face, upper chest and back, but may be more generalized or severe (NCI-CTC Grade 3 or 4) with desquamation. Skin reactions may occur or worsen in sun exposed areas; therefore, the use of sunscreen or avoidance of sun exposure is recommended. Associated symptoms may include itching, tenderness and/or burning. Also, hyperpigmentation or dry skin with or without digital skin fissures may occur. Hair and nail disorders including alopecia, hirsutism, eyelash/eyebrow (see above) changes, paronychia and brittle and loose nails have been reported. **Other Disorders** Epistaxis was also reported in both the single-agent NSCLC and the pancreatic cancer clinical trials. 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 *[see Use in Specific Populations (8.5 and 8.6)]*. The safety of TARCEVA appears similar in Caucasian and Asian patients. **Post-marketing Experience** The following adverse reactions have been identified during post approval use of TARCEVA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders Hair and nail changes, mostly non-serious e.g. hirsutism, eyelash/eyebrow changes, paronychia and brittle and loose nails. Bullous, blistering and exfoliative skin conditions have been reported including cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis *[see Warnings and Precautions (5.6)]*. **Gastrointestinal Disorders** Gastrointestinal perforations *[see Warnings and Precautions (5.5)]*. **Hepatic Disorders** Hepatic failure has been reported in patients treated with single-agent TARCEVA or TARCEVA combined with chemotherapy *[see Warnings and Precautions (5.3)]*. **DRUG INTERACTIONS** Erlotinib is metabolized predominantly by CYP3A4, and inhibitors of CYP3A4 would be expected to increase exposure. Co-treatment with the potent CYP3A4 inhibitor ketoconazole increased erlotinib AUC by 2/3. When TARCEVA was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2, the erlotinib exposure [AUC] and maximum concentration [C_{max}] increased by 39% and 17% respectively. 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), voriconazole and grapefruit or grapefruit juice. *[see Dosage and Administration (2.3)]*. Pre-treatment with the CYP3A4 inducer rifampicin for 7 days prior to TARCEVA decreased erlotinib AUC by about 2/3 to 4/5, which is equivalent to a dose of about 30 to 50 mg in NSCLC patients. In a separate study, treatment with rifampicin for 11 days, with co-administration of a single 450 mg dose of TARCEVA on day 8 resulted in a mean erlotinib exposure (AUC) that was 57.6% of that observed following a single 150 mg TARCEVA dose in the absence of rifampicin treatment *[see Dose Modifications (2.3)]*. Use of alternative treatments lacking CYP3A4 inducing activity is strongly recommended. If an alternative treatment is unavailable, adjusting the starting dose 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 inducers. Other CYP3A4 inducers include, but are not limited to, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital and St. John's Wort *[see Dosage and Administration (2.3)]*. Cigarette smoking has been shown to reduce erlotinib AUC. Patients should be advised to stop smoking; however, if they continue to smoke, a cautious increase in the dose of TARCEVA 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 *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*. Pretreatment and co-administration of TARCEVA decreased the AUC of CYP3A4 substrate, midazolam, by 24%. The mechanism is not clear. In a study, there were no significant effects of gemcitabine on the pharmacokinetics of erlotinib nor were there significant effects of erlotinib on the pharmacokinetics of gemcitabine. Drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and reduce its bioavailability. Increasing the dose of TARCEVA when co-administered with such agents is not likely to compensate for the loss of exposure. Co-administration of TARCEVA with omeprazole, a proton pump inhibitor, decreased the erlotinib AUC by 46%. Since proton pump inhibitors affect pH of the upper GI tract for an extended period, separation of doses may not eliminate the interaction. The concomitant use of proton pump inhibitors with TARCEVA should be avoided if possible. Co-administration of TARCEVA with 300 mg ranitidine, an H_2 receptor antagonist, decreased erlotinib AUC by 33%. When TARCEVA was administered with ranitidine 150 mg twice daily (at least 10 h after the previous ranitidine evening dose and 2 h before the ranitidine morning dose), the erlotinib AUC decreased by 15%. If patients need to be treated with an H_2-receptor antagonist such as ranitidine, it should be used in a staggered manner. TARCEVA must be taken once a day, 10 hours after the H_2-receptor antagonist dosing and at least 2 hours before the next dose of H_2-receptor antagonist. 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. *[see Clinical Pharmacology (12.3)]*. **Pediatric Use** The safety and effectiveness of TARCEVA in pediatric patients have not been established. **OVERDOSAGE** Single oral doses of TARCEVA up to 1,000 mg in healthy subjects and weekly doses 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 reactions, such as diarrhea, rash, and liver transaminase elevation, may occur above the recommended dose *[see Dosage and Administration (2)]*. In case of suspected overdose, TARCEVA should be withheld and symptomatic treatment instituted. **Manufactured for:** OSI Pharmaceuticals, LLC, Farmingdale, NY 11735 an affiliate of Astellas Pharma US, Inc. **Manufactured by:** Kremers Urban Pharmaceuticals, Inc., Seymour, IN 47274 **Distributed by:** Genentech USA, Inc. 1 DNA Way, South San Francisco, CA 94080-4990. For further information please call 1-877-TARCEVA (1-877-827-2382).

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Randomized Phase III Placebo-Controlled Trial of Carboplatin/Paclitaxel With or Without the Vascular Disrupting Agent Vadimezan in Advanced NSCLC

Lara and colleagues presented results from the randomized, placebo-controlled, global, phase III ATTRACT-1 (Antivascular Targeted Therapy: Researching ASA404 in Cancer Treatment) trial, which evaluated the addition of the vascular disrupting agent ASA404 (vadimezan) to paclitaxel-carboplatin (PC) in patients with advanced non–small-cell lung cancer (NSCLC).[1]

Vascular disrupting agents are a new class of cancer therapy designed to interfere with the tumor vasculature by destroying the blood vessels that provide nutrients to solid tumors, leading to tumor necrosis. The vascular disrupting agent ASA404 is a small molecule that exerts direct effects on the epithelial cells of tumor blood vessels, causing apoptosis. In vitro studies have shown that ASA404 causes release of von Willebrand factor and production of cytokines, leading to a loss of integrity of the vasculature. These events culminate in hemorrhagic tumor necrosis. Although the effects of ASA404 have been identified, the molecular target of ASA404 remains unknown.

After preclinical studies showed synergy between ASA404 and taxanes, a randomized phase Ib/II trial was conducted evaluating the efficacy and safety of chemotherapy with or without ASA404 in patients with previously untreated advanced NSCLC.[2] In this study, conducted in 59 patients with advanced NSCLC, the addition of ASA404 at a dose of 1,200 mg/m^2 to carboplatin (area under the time concentration curve [AUC] 6) and paclitaxel (175 mg/m^2) suggested an improvement in partial response (PR) rate (31.2% vs 22.2%), median time to progression (TTP; 5.4 vs 4.4 months), and overall survival (OS; 14.0 vs 8.8 months).

In a phase II extension study, 30 patients received a higher dose of ASA404 (1,800 mg/m^2) plus paclitaxel and carboplatin. The combination was associated with a PR rate of 37.9%, a median TTP of 5.5 months, and a median OS of 14.9 months. In regard to safety, the agent appeared to have minimal toxicity. The incidences of adverse events, deaths, and discontinuations due to adverse events were similar between arms. Moreover, no differences in activity were noted between arms.

These results provided the rationale for studying ASA404 in a phase III trial. The ATTRACT-1 trial was therefore undertaken, in which 1,299 patients with previously untreated stage IIIB/IV NSCLC were randomly assigned to ASA404 (1,800 mg/m^2) plus paclitaxel (200 mg/m^2) and carboplatin (AUC 6; 649 patients) or PC alone (650 patients). Patients with responses or stable disease after 6 cycles received blinded maintenance therapy with ASA404. The trial was open to patients with any NSCLC histology, a performance status of 0 or 1, and adequate end-organ function. Characteristics were well balanced between arms in regard to age, sex, race, performance status, histology, and disease stage. The median age was 61 years; 62% were male; 20% had squamous histology; and 91.4% had stage IV disease. Caucasians comprised 71.5% of the population, and 25% were of Asian descent. Patients were stratified based on histology (nonsquamous vs squamous) and sex.

Treatment delivery outcomes were similar between arms. Patients received a median of 5 cycles (range, 1–6). The median number of maintenance cycles was 3 (range, 1–17) in the PC plus ASA404 arm and 4 (range, 1–16) in the PC arm. The 2 arms were similar in regard to the proportion of patients requiring a dose reduction (55% and

49%, respectively) or dose delay (46% and 50%, respectively) and the median duration of exposure (15 and 16 weeks, respectively).

After a median follow-up of 15 months, there was no significant difference between arms in the primary endpoint of OS, with a median OS of 13.4 months with ASA404 plus PC and 12.7 months with PC alone (hazard ratio [HR], 1.008; *P*=.535). The 2 arms were also similar in regard to median PFS (5.5 months in both arms) and overall response rate (ORR; 24.7% and 24.6%, respectively). Subset analyses showed no patient population in which ASA404 had a benefit, including by geographic region, smoking status, performance status, disease stage, histology, sex, or age.

There was no significant difference in adverse events between arms. The most common adverse events were neutropenia, occurring in 56.8% of patients receiving ASA404 plus PC and 50.7% of patients receiving PC alone. The incidence of grade 4 neutropenia was higher in ASA404-treated patients (26.6% vs 19.0% in the control arm). Other common adverse events included alopecia (47.2% and 48.5%, respectively), nausea (39.7% and 40.2%, respectively), and fatigue (35.6% and 35.0%, respectively).

No overt toxicities that may be expected with the use of a vascular disrupting agent, such as increased hemoptysis, vascular toxicity, or cardiac toxicity, were noted. Moreover, the rate of on-treatment deaths was similar between arms (28 with ASA404 and 25 with placebo). Three deaths were deemed to be study drug–related, including 1 myocardial infarction in a patient receiving ASA404, 1 cerebrovascular accident in a patient receiving placebo, and 1 death due to unknown cause in the placebo arm. The investigators noted no clustering of specific events leading to death in either arm. Moreover, post-protocol systemic therapies were similar between arms.

ABSTRACT SUMMARY **A Phase III Randomized Trial of Adjuvant Chemotherapy With or Without Bevacizumab for Completely Resected Early-Stage NSCLC**

Wakelee and colleagues presented interim safety results of the randomized E1505 trial, which is evaluating the efficacy and safety of adding bevacizumab to adjuvant chemotherapy in patients with resected stage IB–IIIA NSCLC. The chemotherapy regimen consists of doublet therapy with cisplatin (75 mg/m^2 on day 1) plus vinorelbine (30 mg/m^2 on days 1, 8), docetaxel (75 mg/m^2 on day 1), gemcitabine (1,200 mg/m^2 on days 1, 8), or pemetrexed (500 mg/m^2 on day 1), administered in 3-week cycles for 4 cycles. Patients are randomly assigned to chemotherapy alone or with bevacizumab, administered at 15 mg/kg on day 1 every 3 weeks, for up to 1 year.

The trial plans to enroll 1,500 patients. The investigators noted that enrollment onto the trial has been steady and is expected to be complete in 2013. The current analysis included 636 patients who registered between August 2007 and April 26, 2010. This cutoff date was selected to ensure that the analysis was limited to patients who had completed protocol therapy. The safety analysis included an additional 95 patients who were treated but ineligible for the efficacy analysis, primarily due to inadequate lymph node sampling.

Patient characteristics were well balanced between groups; the median age is 61 years (range, 35–86 years); 61% had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0; 51% were female; and 88% were Caucasian. Histology was adenocarcinoma in 54%; disease stage was distributed between IB (24%), II (44%), and IIIA (32%).

The interim safety analysis showed no unexpected toxicities. The incidence of grade 3/4 toxicity was significantly increased with bevacizumab plus chemotherapy versus chemotherapy alone, both overall (84.6% vs 68.8%; *P*<.001) and in regard to several specific adverse events, including hypertension (20.7% vs 2%; *P*<.001), proteinuria (2.9% vs 0.6%; *P*=.035), and abdominal pain (4.3% vs 0.3%; *P*=.001). There was no increased risk of deaths due to toxicity (3.3% vs 2.2%).

The investigators noted that inadequate nodal sampling and lack of interest in 1 year of therapy have presented challenges to study enrollment.

Several explanations for the negative phase III trial results were proposed. First, the small number of patients enrolled in the phase II trial may have overestimated the activity of ASA404. Second, the phase II study design, without a placebo control or blinding, may have affected outcomes. Third, the median survival in this trial—12.7 months in the control arm—exceeded the survival assumptions. The study was only powered to detect a 20% difference in survival between arms from 9 months with chemotherapy to 11.25 months with chemotherapy plus ASA404.

Dr. Lara suggested several possible explanations for the better-than-expected outcomes in the control arm, including chance, stage migration,

improved post-protocol treatments, the relatively high proportion of Asian patients (in whom survival outcomes are typically better), and the paclitaxel dosing used (200 mg/m^2 vs 175 mg/m^2 in the phase II trial). The development of ASA404 has now been halted. Dr. Lara noted that further development of the agent is contingent upon the identification of the molecular target of ASA404.

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PARAMOUNT: Pemetrexed Plus Best Supportive Care for Advanced Nonsquamous NSCLC

Paz-Ares and colleagues presented results of the randomized, placebo-controlled, double-blind, phase III PARAMOUNT trial, which evaluated the role of maintenance pemetrexed immediately after pemetrexed/cisplatin induction therapy in patients with advanced nonsquamous NSCLC.[1] Previous studies have demonstrated the efficacy of pemetrexed in the treatment of patients with advanced, nonsquamous NSCLC, both in combination with cisplatin in previously untreated patients[2] and as maintenance therapy[3] following platinum doublet therapy. However, the use of pemetrexed maintenance therapy following pemetrexed-containing induction therapy had not been evaluated in a phase III study.

The PARAMOUNT trial enrolled 939 patients with previously untreated stage IIIB or IV nonsquamous NSCLC and an ECOG PS of 0 or 1. Patients received induction therapy consisting of pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) administered on day 1, every 3 weeks for up to 4 cycles. Those without progressive disease after induction therapy were stratified by performance status (or vs 1), disease stage at baseline (IIIB vs IV), and response to induction (complete response [CR]/PR vs stable disease) and randomly assigned 2:1 to maintenance pemetrexed (500 mg/m^2 on day 1, every 21 days) plus best supportive care or placebo plus best supportive care. Treatment was continued until disease progression. Patients in both arms received folic acid and vitamin B_{12} supplementation.

Of the 939 patients enrolled, 539 patients entered the randomized part of the study. The remaining 400 patients were not randomized due to progressive disease (217 patients), adverse events (62 patients), death (56 patients), or other reasons (65 patients). For the maintenance phase, 359 patients were assigned to pemetrexed and 180 were assigned to placebo. At the data cutoff, 38% of patients were still on pemetrexed maintenance and 24% were still on placebo.

Patient characteristics were well balanced between arms. The median age was 61 years, 60% were male, 95% were Caucasian, 80% were prior smokers, 33% had a performance status of 0, and 90% had stage IV disease. Nearly half of patients (45%) attained a CR or PR after induction therapy, while the remainder had stable disease.

Although the median number of maintenance cycles completed was the same between arms (4 cycles), the proportion of patients completing more than 6 cycles was higher with pemetrexed versus placebo (23% vs 14%).

The primary endpoint, investigator-assessed PFS from date of randomization (after completing induction chemotherapy), was significantly improved with pemetrexed versus placebo, with a median PFS of 4.1 months and 2.8 months, respectively (unadjusted HR, 0.62; 95% CI, 0.49–0.79; *P*=.00006). An independent review, performed in 88% of randomized patients, showed similar results, with a median PFS of 3.9 months and 2.6 months, respectively (unadjusted HR, 0.64; 95% CI, 0.51–0.81; *P*=.0002). The investigator-assessed median PFS from the start of induction therapy was 6.9 months with pemetrexed and 5.6 months with placebo (unadjusted HR, 0.59; 95% CI, 0.47–0.74; *P*<.00001).

The ORR in the maintenance phase was not significantly different between arms (2.8% vs 0.6%), though significantly more pemetrexed-treated patients maintained stable disease, for a disease control rate of 71.8% versus 59.6% with placebo (*P*=.009). Although the trial was powered to detect differences in OS, data were not available at this analysis due to a death rate that was lower than expected. Therefore, survival outcomes are forthcoming.

Health-related quality of life outcomes, assessed at baseline, at day 1 of each treatment cycle, and at 30 days post-continuation, were not significantly different between arms. Subgroup analysis suggested that the benefit of pemetrexed was observed across subgroups.

An International, Randomized, Placebo-Controlled, Double-Blind Phase III Study (MONET1) of Motesanib Plus Carboplatin/Paclitaxel in Patients With Advanced Nonsquamous NSCLC

Scagliotti and colleagues presented results from the international, randomized, placebo-controlled, double-blind phase III MONET1 (Motesanib NSCLC Efficacy and Tolerability) study, which evaluated the safety and efficacy of adding motesanib to CP in patients with advanced nonsquamous NSCLC. Motesanib is a selective multitargeted oral inhibitor with activity against VEGF receptors 1, 2, and 3; platelet-derived growth factor receptor (PDGFR), and Kit. In a phase II study, motesanib 125 mg once daily appeared to have similar efficacy as bevacizumab in patients with advanced nonsquamous NSCLC.

The current study enrolled patients with unresectable stage IIIB NSCLC with pericardial or pleural effusion or stage IV/recurrent nonsquamous NSCLC. The study was initially open to patients with squamous histology, but an increased incidence of gross hemoptysis in these patients led to a protocol amendment limiting enrollment to patients with nonsquamous histology. A total of 1,090 patients were randomly assigned to carboplatin (AUC 6 mg/mL/min) and paclitaxel (200 mg/m^2) plus either motesanib 125 mg once daily (541 patients) or placebo once daily (549 patients). Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent.

After a median follow-up of 45–48 weeks, there was no difference in median OS with motesanib plus CP versus placebo plus CP in patients with nonsquamous NSCLC (13.0 vs 11.0 months; HR, 0.90; 95% CI, 0.78–1.04; *P*=.14) or in the subset of patients with adenocarcinoma (13.5 vs 11.0 months; HR, 0.88; 95% CI, 0.75–1.03; *P*=.11). The addition of motesanib to CP was associated with a significant improvement in median PFS over chemotherapy alone in patients with nonsquamous histology (5.6 vs 5.4 months; HR, 0.79; 95% CI, 0.68–0.90; *P*=.0006), with a similar benefit in patients with adenocarcinoma.

Among patients with nonsquamous histology and measurable disease at baseline, the addition of motesanib to chemotherapy was associated with a significant increase in ORR over chemotherapy alone (40% vs 26%; *P*<.0001). There was no significant association between pharmacodynamic changes in placental growth factor and OS.

Motesanib was associated with an increased incidence of adverse events. The most frequently observed grade 3 or higher adverse events were neutropenia (5% with motesanib plus CP vs 2% with CP alone), diarrhea (5% vs <1%), febrile neutropenia (4% vs 3%), pneumonia (4% vs 1%), and dehydration (4% vs <1%).

In conclusion, this study showed no significant survival improvement with the addition of motesanib to carboplatin and paclitaxel in patients with nonsquamous NSCLC. However, the investigators suggested that motesanib was active, given the improvement in PFS and ORR in patients receiving the agent compared with those receiving placebo.

In regard to safety, pemetrexed was associated with an increased incidence of drug-related serious adverse events compared with placebo (8.9% vs 2.8%) but no increase in drug-related deaths (0.6% in both arms). Rates of discontinuation due to adverse events were 5.3% and 3.3%, respectively. Patients receiving pemetrexed were more likely than those receiving placebo to develop a grade 3/4 drug-related laboratory toxicity (9.2% vs 0.6%) or a grade 3 or higher nonlaboratory toxicity (8.9% vs 4.4%).

No single adverse event occurred at grade 3/4 severity in more than 5% of patients. The most common grade 3/4 toxicities associated with pemetrexed, which all occurred significantly more frequently with pemetrexed than placebo, were fatigue (4.2% vs 0.6%), anemia (4.5% vs 0.6%), and neutropenia (3.6% vs 0%).

Overall, the trial demonstrated a significant PFS improvement with the use of pemetrexed maintenance therapy in patients with advanced nonsquamous NSCLC receiving first-line pemetrexed/cisplatin induction therapy. The toxicity profile was similar to that shown in the previous trial of maintenance pemetrexed in NSCLC.[3]

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Interim Results of the European Erlotinib Versus Chemotherapy (EURTAC) Phase III Randomized Trial

Rosell and colleagues presented results of the randomized, phase III European Erlotinib Versus Chemotherapy (EURTAC) trial, which compared erlotinib versus standard chemotherapy in the first-line setting.[1] This trial was initiated based on a previous study that demonstrated the feasibility of large-scale screening for epidermal growth factor receptor (EGFR) mutations and showed the activity of erlotinib in patients testing EGFR mutation–positive.[2]

The study enrolled patients with no previous chemotherapy treatment, stage IIIB or IV NSCLC, an EGFR exon 19 deletion or an exon 21 L858R mutation, an ECOG PS of 0–2, and adequate organ function. EGFR mutation screening was performed based on samples obtained through laser capture microdissection. DNA sequencing was first done using Sanger sequencing and then confirmed in a central laboratory using TaqMan® for exon 21 and GeneScan® for exon 19.

Patients were randomly assigned to erlotinib 150 mg/day until disease progression or to platinum-based doublet chemotherapy administered every 3 weeks for 4 cycles. Stratification was based on performance status and EGFR mutation type.

A total of 1,227 patients were screened for EGFR mutations, and 21% of patients tested EGFR mutation–positive. As of January 26, 2011, 174 patients were randomized to erlotinib (86 patients) or chemotherapy (88 patients). One patient in the chemotherapy arm received treatment before randomization and was therefore excluded from the intent-to-treat population. The median follow-up was 18.9 months in the erlotinib arm and 14.4 months in the chemotherapy arm.

The median age of enrolled patients was 65 years; the majority of patients were female (67% in the erlotinib arm and 78% in the chemotherapy arm) and were never-smokers (66% and 72%, respectively). Overall, approximately two-thirds of patients had the exon 19 deletion and one-third had the L858R mutation. Approximately one-third of patients had an ECOG PS of 0, and 14% had an ECOG PS of 2. Patients had a median of 2 metastatic sites.

In an interim analysis of 153 patients, the primary endpoint (PFS) was significantly superior with erlotinib versus chemotherapy, with a median PFS of 9.4 months and 5.2 months, respectively (HR, 0.42; 95% CI, 0.27–0.64; *P*<.0001), in an intent-to-treat analysis. The updated analysis of all 174 patients confirmed the benefit of erlotinib, with a median PFS of 9.7 months versus 5.2 months with chemotherapy (HR, 0.37; 95% CI, 0.25–0.54; *P*<.0001).

Subgroup analysis showed some variations in the benefit of erlotinib in different groups, including a greater benefit in patients with a lower performance status, in never-smokers, and in patients with exon 19 deletions (Table 1).

Erlotinib was also associated with greater objective responses than chemotherapy, including a higher ORR (58% vs 15%) and a higher disease control rate (79% vs 66%). An interim analysis of OS showed no significant improvement in survival with erlotinib versus chemotherapy (HR, 0.80; 95%

Table 1. Subgroup Analyses of PFS Outcomes With Erlotinib Versus Chemotherapy in EGFR-Mutated Advanced Non–Small-Cell Lung Cancer

Subgroup	Number of Patients	HR for PFS With Erlotinib vs Chemotherapy (95% CI)
All patients	173	0.37 (0.25–0.54)
Age		
<65 years	85	0.44 (0.25–0.75)
≥65 years	55	0.28 (0.16–0.51)
Sex		
Male	47	0.38 (0.17–0.84)
Female	126	0.35 (0.22–0.55)
ECOG PS		
0	57	0.26 (0.12–0.59)
1	92	0.37 (0.22–0.62)
2	24	0.48 (0.15–1.48)
Smoking status		
Current smoker	19	0.56 (0.15–2.15)
Former smoker	34	1.05 (0.40–2.74)
Never smoker	120	0.24 (0.15–0.39)
EGFR mutation		
Exon 19 deletion	115	0.30 (0.18–0.50)
858R mutation	58	0.55 (0.29–1.02)

CI=confidence interval; ECOG PS=Eastern Cooperative Oncology Group performance status; EGFR=epidermal growth factor receptor; PFS=progression-free survival.

CI, 0.47–1.37; *P*=.42). However, there was substantial crossover from the control arm to erlotinib upon disease progression. Of the 59 patients in the chemotherapy arm with a PFS event, 51 had second-line treatment, which consisted of an EGFR tyrosine kinase inhibitor (TKI) in 49 patients.

Safety analysis showed a superior toxicity profile with erlotinib versus chemotherapy, including a lower rate of grade 3/4 adverse events (45% vs 81%), a lower incidence of dose modifications or interruptions due to treatment-related adverse events (23% vs 47%), a lower incidence of discontinuations due to treatment-related adverse events (5% vs 14%), and a lower rate of treatment-related serious adverse events (7% vs 16%). Grade 3/4 adverse events observed with erlotinib included rash (9%), alanine aminotransferase elevations (5%), and diarrhea (4%).

In summary, this phase III trial provided prospective evidence in a Caucasian population of the benefit of erlotinib over chemotherapy in the first-line treatment of patients with EGFR mutation–positive NSCLC. In this trial, erlotinib was associated with a 63% reduction in the risk of disease progression or death, and showed no new safety concerns.

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Phase II Trial of Erlotinib/Bevacizumab Compared With Cisplatin/Gemcitabine Plus Bevacizumab in First-Line Treatment of Advanced NSCLC

Thomas and colleagues presented results from the randomized, phase II INNOVATIONS trial, which compared bevacizumab plus erlotinib versus gemcitabine/cisplatin plus bevacizumab in the first-line treatment of patients with previously untreated stage IIIb/IV nonsquamous NSCLC.[1]

Combination therapy with the antiangiogenic agent bevacizumab and the EGFR TKI erlotinib had previously been evaluated in nonrandomized trials. Herbst and colleagues[2] conducted a phase I/II study evaluating bevacizumab/erlotinib in patients with recurrent NSCLC. The study enrolled 40 patients with stage IIIb/IV disease who had previously received at least 1 platinum-based regimen. Bevacizumab/erlotinib showed activity in this study, with an ORR of 20%, a median PFS of 6.2 months, and a median OS of 12.6 months in the 34 patients who received the phase II dose.

Based on the results of this study, the Acting on Lung Cancer Study group initiated the randomized, phase II INNOVATIONS trial to compare the efficacy and safety of bevacizumab/erlotinib versus chemotherapy plus bevacizumab in patients with previously untreated disease. The inclusion of bevacizumab in the control arm was based on the demonstration of a 12.3- month survival with carboplatin, paclitaxel, and bevacizumab in the ECOG 4599 trial.[3]

Patients were randomly assigned to cisplatin (80 mg/m^2 on day 1), gemcitabine (1.25 g/m^2 on days 1, 8), and bevacizumab (15 mg/kg on day 1 every 22 days), or erlotinib (150 mg daily) plus bevacizumab (15 mg/kg on day 1 every 22 days). Chemotherapy was administered for up to 6 cycles; bevacizumab (on both arms) and erlotinib (on the experimental arm) was continued until disease progression or unacceptable toxicity. Responses were evaluated every 6 weeks.

Between November 2007 and August 2009, 224 patients enrolled on the study. Patient characteristics were well balanced between treatment arms. The median age was 62.5 years on the erlotinib/bevacizumab arm and 59.9 years on the chemotherapy/bevacizumab arm. Histology was predominately adenocarcinoma (86% and 93%, respectively), and most patients had stage IV disease (86% and 81%, respectively). Nearly half of patients had an ECOG PS of 0 (43% in the erlotinib/bevacizumab arm and 47% in the chemotherapy/bevacizumab arm). Information on smoking status was available in more than 95% of patients; 24% of patients were former light smokers or never-smokers.

Dr. Thomas reported results after a median follow-up of 14.3 months, at which time 87% of patients had progressed or died and 54% of patients had died. The median treatment duration was 6 cycles of chemotherapy (16–18 weeks), 5 cycles of bevacizumab (14–15

weeks), and 12.8 weeks of erlotinib. The upper range of erlotinib treatment was 2.6 years (137 weeks). The proportion of patients requiring bevacizumab dose reductions was significantly higher in the chemotherapy arm than in the erlotinib/bevacizumab arm (25% vs 14%).

The primary endpoint, PFS, was significantly longer in the control arm (chemotherapy/bevacizumab) than in the experimental arm (bevacizumab/erlotinib), with a median PFS of 7.7 months and 3.5 months, respectively (HR, 1.77; 95% CI, 1.33–2.36; *P*<.0001). Disease progression was documented in 79% of patients receiving erlotinib/bevacizumab and 75% of patients receiving chemotherapy/bevacizumab. Of these patients, 73% and 76%, respectively, received additional treatment. Subsequent treatment included chemotherapy in 71% and 60%, respectively, and an EGFR TKI in 7% and 41% of patients, respectively. Nearly half of patients (42% and 51%, respectively) received monotherapy, which was predominately pemetrexed. Multiagent chemotherapy was used in 55% and 19% of patients, respectively, receiving subsequent treatment.

There was a trend toward a longer median OS with chemotherapy/bevacizumab versus erlotinib/bevacizumab (16.3 vs 12.6 months; HR, 1.39; 95% CI, 0.97–1.99; *P*=.07). The 12-month survival rate was 54% and 60%, respectively. Dr. Thomas noted that the survival outcome in the control arm was in the range of the best survival times reported for chemotherapy plus bevacizumab. He also pointed out that although erlotinib/bevacizumab was associated with a median OS of 12.6 months, 54% of patients went on to receive chemotherapy. Chemotherapy/bevacizumab was also associated with a significant improvement in ORR compared with erlotinib/bevacizumab (37% vs 13%; *P*<.0001).

A genotype analysis by EGFR status was conducted to determine if any patient subgroups benefitted from erlotinib/bevacizumab. Genotypic data were available for 72% of patients, evenly distributed between the 2 treatment arms. There was no significant difference in the rate of EGFR mutations among patients in the erlotinib/bevacizumab arm (25%) or the chemotherapy/bevacizumab arm (15%). Along with the commonly reported exon 19 deletions and the exon 21 point mutation L858R, additional point mutations at exons 19 and 21 were reported.

Among the 32 patients with EGFR-mutated tumors, the ORR was 25% in both treatment arms. PFS outcomes in these patients were similar between treatment arms, with a median PFS of 4.4 months with erlotinib/bevacizumab and 5.7 months with chemotherapy/bevacizumab (*P*=.87). There was a trend toward a longer median OS with erlotinib/bevacizumab versus chemotherapy/bevacizumab (17.0 vs 10.0 months; HR, 0.41; 95% CI, 0.16–1.06; *P*=.057). Dr. Thomas noted that the number of patients with EGFR-mutated tumors was not large enough to draw any conclusions. However, he suggested that the similar PFS outcomes observed in the 2 arms may indicate that the addition of bevacizumab may limit the efficacy of EGFR TKI activity in these patients.

Among the 129 patients with EGFR wild-type tumors, the ORR was 41% with chemotherapy/bevacizumab and 8% with erlotinib/bevacizumab. The superiority of chemotherapy/bevacizumab over erlotinib/bevacizumab in these patients was significant in regard to median PFS (8.4 vs 3.4 months; HR, 1.88; 95% CI, 1.28–2.75; *P*=.001) and median OS (18.0 vs 10.3 months; HR, 1.70; 95% CI, 1.05–2.76; *P*=.003).

The incidence of hematologic toxicity was 50% in the chemotherapy/bevacizumab arm (32% grade 3/4) and 0% in the erlotinib/bevacizumab arm (*P*<.0001). Specific grade 3/4 hematologic events associated with chemotherapy/bevacizumab included thrombocytopenia (15%), anemia (7%), neutropenia (7%), and febrile neutropenia (2%). In regard to nonhematologic adverse events, erlotinib/bevacizumab was associated with higher rates of grade 3/4 rash than chemotherapy/bevacizumab (15% vs 1%; *P*<.0001) and lower rates of grade 3/4 nausea/vomiting (1% vs 10%; *P*=.003), hypertension (3% vs 10%; *P*=.03), and thromboembolism (5% vs 15%; *P*=.008). Other adverse events occurred at similar rates between arms.

Bleeding events of any grade occurred in 15% of patients in the erlotinib/bevacizumab arm and 28% of patients in the chemotherapy/bevacizumab arm; 1% of events in each arm were grade 3/4. These were primarily epistaxis (10% and 24%, respectively), though 1 patient in the erlotinib/bevacizumab arm died from pulmonary hemorrhage. Treatment-related mortality rates were 6% with erlotinib/bevacizumab and 5% with chemotherapy/bevacizumab. Excluding 3 patients with sudden cardiac death at home, mortality rates were 5% and 3%, respectively.

The investigators concluded that in this group of unselected patients, gemcitabine/cisplatin plus bevacizumab was more effective than erlotinib plus bevacizumab for the first-line treatment of advanced nonsquamous NSCLC.

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Impact of Crizotinib on Survival in Patients With Advanced, ALK-Positive NSCLC

Rearrangement of the anaplastic lymphoma kinase (ALK) gene resulting in an aberrant fusion gene is detectable in a small proportion (approximately 4%) of patients with NSCLC.[1] Typically, the chromosomal rearrangement involves an inversion or translocation, resulting in expression of an oncogenic fusion kinase such as EML4-ALK. The rearrangement is observed primarily in younger patients with adenocarcinoma and a nonsmoking or light-smoking history, and rarely occurs in patients with EGFR or KRAS mutations.[2] Preclinical studies have demonstrated an oncogenic driver activity with ALK fusion proteins, suggesting that ALK could be a therapeutic target.

Crizotinib (previously known as PF-02341066) is the first ALK inhibitor to be evaluated in humans. The agent is a potent, selective, ATP-competitive oral inhibitor of ALK and MET tyrosine kinases. A multicenter phase I study[2] evaluated the safety and activity of crizotinib in an expanded cohort of patients with advanced ALK-positive NSCLC. A total of 82 patients received crizotinib at the maximum tolerated dose of 250 mg twice daily. The objective response rate was 57%, and 33% had stable disease. The median PFS of a larger cohort of patients that includes these patients was 10 months.[3]

Although these results indicate that crizotinib has significant activity in patients with advanced, ALK-positive NSCLC, survival was not previously reported. OS is typically determined through randomized, controlled studies. However, given the expanding number of targeted therapies demonstrating activity in NSCLC, many patients may receive post-study treatments, which confound the survival analysis. Crossover will also likely be an issue in determining survival in the ongoing randomized, phase III trial of crizotinib, as ALK-positive patients in the control arm will cross over to crizotinib upon disease progression.

An alternative method of assessing OS is the use of a historical comparison, in which the survival of patients receiving crizotinib is compared against that of a comparator population of crizotinib-naïve patients with ALK-positive NSCLC. Therefore, Shaw and colleagues compared OS of ALK-positive patients treated with crizotinib against survival of clinically comparable crizotinib-naïve patients.[4] The researchers also evaluated the prognostic value of ALK rearrangement in NSCLC.

To evaluate survival in ALK-positive patients treated with crizotinib, the researchers focused on outcomes in the 56 patients from the phase I trial who were recruited from the United States or Australia. The remaining patients from the phase I study were recruited from Korea and were omitted from the analysis because a Korean ALK-positive control group was not available. The ALK-positive crizotinib-naïve group included 36 patients recruited from the United States and Australia. A third comparator group—the ALK-negative, EGFR wild-type patients—included 253 patients recruited from a single center in the United States

From these 3 groups, survival outcomes were evaluated for the overall population and for subsets based on treatment history. Survival outcomes in ALK-positive crizotinib-treated patients were assessed for the 30 patients receiving second- or third-line therapy. Outcomes in the control groups were assessed in patients receiving second-line therapy, including 23 patients with ALK-positive NSCLC and 125 patients with ALK-negative NSCLC. To account for differences in clinical and pathologic features, the investigators examined outcomes in the subset of patients who were never- or light-smokers with adenocarcinoma (28 ALK-positive, crizotinib-treated patients, 21 ALK-positive, crizotinib-naïve patients, and 48 wild-type patients). Patients were screened for ALK rearrangement by fluorescence in situ hybridization (FISH) performed between December 2007 and February 2010.

Among the 82 ALK-positive patients treated with crizotinib on the phase I trial, the median OS from the first crizotinib dose was not yet reached at the time of analysis. Survival rates at 1 year and 2 years were 74% and 54%, respectively. The 50 patients still alive had been followed for a median of 18 months. No differences in OS were noted based on age, sex, smoking history, or ethnicity. Among the 56 ALK-positive crizotinib-treated patients from the United States and Australia in the phase I trial, the median OS also had not been reached. Nor had the median OS been reached among the subset of 30 patients receiving their second or third line of therapy. In contrast, the median OS of 23 ALK-positive patients not treated with crizotinib was 6 months (HR, 0.36; P=.004; Table 2).

The 1-year and 2-year survival rates were 70% and 55%, respectively, among crizotinib-treated patients and 44% and 12%, respectively, among ALK-positive crizotinib-naïve patients. This significant outcome, which was seen despite similar treatment and disease characteristics between the 2 groups, suggests that crizotinib may significantly extend survival in patients with advanced ALK-positive NSCLC.

The investigators then evaluated the prognostic significance of ALK

Table 2. Outcomes With Crizotinib in ALK-Positive Non–Small Cell Lung Cancer

	Crizotinib-Treated ALK-Positive NSCLC (n=56)	Historical ALK-Positive Controls (N=36)
Median overall survival	Not reached	6 months
1-year overall survival rate	70%	44%
2-year overall survival rate	55%	12%

Note: the hazard ratio and *P* value for median overall survival was 0.36 and .004, respectively.

rearrangement in NSCLC, comparing outcomes in 36 patients with ALK-positive NSCLC versus 253 patients with ALK-negative, EGFR wild-type NSCLC. Consistent with previous reports, ALK-positive patients were significantly younger than wild-type controls (median age, 51 vs 64 years; *P*<.001) and were more likely to be never-smokers (67% vs 25%) or light-smokers (19% vs 13%; *P*<.001 for difference in smoking history). Otherwise, there were few differences between the ALK-positive crizotinib-naïve patients and the wild-type patients. In both groups, patients had received a median of 2 prior therapies.

No significant differences in OS according to ALK status were found. The median OS from second-line therapy was 6 months in ALK-positive patients and 11 months in wild-type patients (HR, 1.42; *P*=.18). Conversely, the median OS was significantly improved in ALK-positive crizotinib-treated patients compared with the wild-type control group (not reached vs 11 months; HR, 0.49; *P*=.02).

In summary, this study suggests that in patients with NSCLC and ALK rearrangements, crizotinib provides a significant survival benefit in the second-line or third-line setting. The study also showed that ALK rearrangement is not a favorable prognostic factor in advanced NSCLC. However, the authors pointed out several limitations that must be considered: first, this was a retrospective, nonrandomized study, and therefore imbalances in the study populations cannot be ruled out. Second, patient numbers in subset analyses were small. Finally, the use of post-crizotinib therapies may have confounded survival outcomes. Keeping these caveats in mind, these findings indicate that crizotinib may improve survival for patients with ALK-positive NSCLC.

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Efficacy, Tolerability, and Biomarker Analysis From a Study of Gefitinib as Maintenance Therapy in Patients With NSCLC

Multiple clinical trials have shown that maintenance therapy with an EGFR tyrosine kinase inhibitor is associated with improved PFS in selected patients with NSCLC who respond to first-line therapy. The multicenter, randomized, parallel-group, placebo-controlled, phase III INFORM trial (also called the Chinese Thoracic Oncology Group study 0804) was designed to evaluate the benefit of gefitinib maintenance therapy in patients with NSCLC who have disease control after first-line platinum-based chemotherapy.[1]

The trial enrolled patients with measurable stage IIIB/IV disease who had completed 4 cycles of first-line platinum-based chemotherapy without progressive disease or unacceptable toxicity. Patients had a life expectancy of at least 12 weeks and a World Health Organization performance status of 0–2. Between September 2008 and August 2009, 296 patients enrolled on the study from 27 centers across China. Patients were randomly assigned to

gefitinib 250 mg/day (148 patients) or placebo once daily (148 patients).

Overall, the baseline characteristics were well balanced between the 2 treatment arms. The median age was 54 years; 54% were never-smokers; 71% had adenocarcinoma; and 75% had stage IV disease. First-line taxane-based chemotherapy was used in 43% of patients, and 37% attained a response to first-line therapy.

After a median follow-up of 17 months, gefitinib was associated with a significant 58% improvement in PFS compared with placebo (median PFS, 4.8 vs 2.6 months; HR, 0.42; 95% CI, 0.33–0.55; *P*<.0001) in an intent-to-treat analysis. Gefitinib was also associated with a superior objective response rate (23.6% vs 0.7%; *P*=.0001) and disease control rate (71.6% vs 50.7%; *P*=.0001) compared with placebo.

There was no significant difference in OS between arms. The median OS was 18.7 months on the gefitinib arm and 16.9 months on the placebo arm (HR, 0.84; 95% CI, 00.62–1.14; *P*=.26); 12-month survival rates were 68.8% and 66.0%, respectively. The investigators noted an imbalance in post-discontinuation treatment between arms, with gefitinib-treated patients less likely than placebo-treated patients to receive subsequent targeted therapy (8.1% vs 31.8%) or chemotherapy (39.9% vs 53.4%).

The incidence of treatment-related adverse events was higher with gefitinib compared to placebo (66.7% vs 23.0%), but serious adverse events were uncommon (2.0% vs 0%). Grade 3 or higher adverse events occurred in 6.8% of patients receiving gefitinib. Interstitial lung disease–type adverse events developed in 2 patients, including 1 who died from the adverse event. The most common toxicities associated with gefitinib were skin rash (49.7% vs 9.5% with placebo), diarrhea (25.2% vs 8.8%), ALT elevations (22.1% vs 8.1%), and AST elevations (14.3% vs 4.1%). Serious adverse events included 3 patients with ALT elevations (2.0%) and 1 patient with an AST elevation (0.7%).

Collection of tumor samples for biomarker analysis was not mandatory in the study, although nearly all patients gave consent for analysis. Overall, 79 samples (27%) were evaluable for EGFR mutation analysis, and mutations were detected in 30 samples (38.0%). In the subset of patients with known EGFR mutation status, baseline characteristics were similar to those of the overall population. Among patients with EGFR mutations, the median PFS was 16.6 months with gefitinib and 2.8 months with placebo (HR, 0.17; 95% CI, 0.07–0.42). Among patients with wild-type EGFR, the median PFS was 2.7 months with gefitinib and 1.5

Initial Phase II Results With Crizotinib in Advanced ALK-Positive Non–Small-Cell Lung Cancer: PROFILE 1005

Crinò and colleagues presented preliminary results of an ongoing open-label, multicenter, phase II study of crizotinib in patients with advanced ALK-positive NSCLC. The study plans to enroll 400 patients who have progressed after at least 1 prior platinum-based chemotherapy regimen for recurrent, advanced, or metastatic disease. Patients are receiving crizotinib 250 mg twice daily administered continuously in 3-week cycles. Results were presented for the first 136 evaluable patients. The median age of the cohort is 52 years (range, 29–82 years); 47% are male. In regard to ethnicity, patients are primarily Caucasian (63%) and Asian (32%). Patients are mostly never-smokers (68%) or former smokers (29%) with adenocarcinoma (96%). Most patients (93%) had received at least 2 prior chemotherapy regimens (range, 1–11).

Of 133 patients evaluable for efficacy, the ORR was 51.1%, and the disease control rate at week 12 was 73.7%. Moreover, clinically meaningful improvements in pain, cough, dyspnea, and fatigue were observed as early as cycle 2 and were maintained during treatment. Crizotinib was associated with increases in nausea/vomiting, constipation, and diarrhea. However, the only clinically meaningful impairments were constipation at cycle 2 and diarrhea at cycle 3. Quality of life was maintained during therapy, and a clinically meaningful improvement was reported at cycle 7.

Treatment-related adverse events were primarily mild to moderate. Adverse events occurring in at least 30% of patients included visual effects (59%), nausea (57%), diarrhea (43%), and vomiting (42%). The most common grade 3 adverse events were increases in alanine aminotransferase (ALT) levels (7%) and fatigue (2%). Adverse events causing treatment discontinuation included ALT increases (3 patients) and pneumonitis (2 patients). Two deaths were considered treatment-related—1 due to pneumonitis and 1 unknown.

Overall, these findings continue to show significant antitumor activity with crizotinib in patients with ALK-positive advanced NSCLC, with safety findings similar to those previously reported.

months with placebo (HR, 0.86; 95% CI, 0.48–1.51). PFS outcomes among the subset of patients with unknown EGFR mutation status were similar to those of the overall population, with a median PFS of 6.0 months with gefitinib and 2.7 months with placebo (HR, 0.40; 95% CI, 0.29–0.54).

Dr. Zhang noted that this was the first randomized trial of maintenance therapy to be conducted in an Asian population with advanced NSCLC. In patients with advanced NSCLC with stable disease after first-line chemotherapy, maintenance gefitinib provided a significant PFS benefit and was well tolerated.

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Identification of Driver Mutations in Tumor Specimens From 1,000 Patients With Lung Adenocarcinoma

The identification of driver mutations in lung cancer, such as EGFR and EML4-ALK, has transformed the treatment of patients with NSCLC. As new oncogenic drivers have been identified and agents targeting those drivers have been developed, it has become important to identify patients whose tumors have involvement of these driver mutations. This knowledge is important for making therapeutic decisions and for identifying patients who may be eligible for clinical trials. Indeed, the National Comprehensive Cancer Center (NCCN)[1] and ASCO[2] guidelines now recommend mutation testing for EGFR mutations at diagnosis of nonsquamous NSCLC.

The Lung Cancer Mutation Consortium (LCMC) is a research effort funded through a Grand Opportunity Grant from the American Recovery and Relief Act. The consortium, which includes researchers from 14 academic centers, was formed with the goal of testing 1,000 tumor specimens from patients with lung adenocarcinoma for the presence of 10 driver mutations: *KRAS, EGFR, BRAF, HER2, PIK3CA, AKT1, NRAS, MEK1,* and *EML4-ALK,* and *MET* amplification. This information would be used to select erlotinib for patients with EGFR mutations or to recommend a clinical trial of an agent targeting specific mutations.[3]

In regard to logistics, genotype testing was performed at all 14 research sites. Although some sites shared specimens, the goal was to establish a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory at each site where testing could be continued after the completion of the grant.

The study included 1,000 patients with stage IV lung adenocarcinoma with an ECOG PS of 0–2 and with sufficient tissue to perform genotypic testing. Central pathology review to confirm adenocarcinoma was performed at MD Anderson Cancer Center, and mutation analyses were done in a CLIA-certified lab at individual sites, whenever possible. Results were reported to a central database created by the National Cancer Institute (NCI) and reported to the treating physician, who could then use this information as best as possible. Patients could be selected for erlotinib treatment, or could be directed to an appropriate clinical trial, if available. The consortium also aimed to establish linked trials for specific mutations.

As of May 2011, 1,234 patients had consented to enrollment and 14% were ineligible, primarily due to inadequate tissue on the pathology review. The eligible group includes 1,064 patients. Complete mutational analysis, which includes FISH analysis for MET and ALK and mutation profiling for the remaining mutations, was performed on 516 specimens.

Mutations were identified in 54% of tumors that were fully tested. The most common mutations were KRAS (22%), EGFR (17%), and EML4-ALK (7%). Multiple mutations were rare; 97% of mutations were mutually exclusive, with only 14 of 516 mutations occurring in combination. The 2 aberrations that were more likely to occur in the presence of other mutations were MET amplification and PIK3CA mutations.

The development of mutation testing capability at each consortium site was an important goal of the grant. At the beginning of the grant, only 4 institutions had mutational testing capability; this has since increased to 11 sites. These sites will continue to function after the completion of the grant, serving as a resource for research and patient care.

Another goal of the consortium is to link trials to identified mutations. These are industry-sponsored trials that were not organized by the consortium, but instead are linked to the consortium. Currently, the LCMC is linked with 8 trials. Affiliated studies are investigating erlotinib plus OSI 906 and erlotinib plus MM 121 for patients with EGFR mutations; tivantinib plus erlotinib and GSK1120212 for patients with KRAS mutations; crizotinib (for EML4-ALK); GSK1120212 (for NRAS, MEK1, and BRAF [not V600E]); GSK2118434 (for BRAF [V600E]), afatinib (for HER2), and BKM120 (for PIK3CA).

Dr. Kris also reviewed the data from a single institution to provide an example of the workflow and results. At the Memorial Sloan-Kettering Cancer Center, 121 patients were enrolled and 102 had complete multiplex mutation testing and/or FISH data. Driver mutations were identified in 60 patients (59%), and 31 patients (30%) received therapy targeted to a specific mutation; this included erlotinib as initial therapy in 19 patients and a clinical trial of a targeted agent in 16 patients.

In summary, the LCMC efforts showed that more than half of patients with lung adenocarcinoma have a detectable actionable driver mutation. Mutation testing can be used in real-time to select erlotinib as initial therapy and to direct patients to appropriate clinical trials based on detected mutations. Moreover, new mutations could be easily added to the multiplexed process. After the current grant ends, the LCMC investigators plan to maintain the consortium and expand its scope.

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An Open-Label Phase II Study of the Hsp90 Inhibitor Ganetespib (STA-9090) as Monotherapy in Patients With Advanced NSCLC

Preclinical studies have shown a rationale for heat shock protein (Hsp)90 inhibition as a therapeutic strategy in NSCLC. In vitro, Hsp90 inhibition suppresses mutant EGFR signaling, including in cells with the secondary T790M mutation.[1] KRAS mutations are associated with enhanced Hsp90 dependency, and KRAS-mutant NSCLC cell lines have demonstrated high response to Hsp90 inhibitors.[2] Moreover, other NSCLC subsets are driven by oncogenes that are Hsp90 clients, including mutant HER2, mutant BRAF, and EML4-ALK.[3,4]

Ganetespib (STA-9090) is a potent Hsp90 that is not structurally related to the first-generation ansamycin class of Hsp90 inhibitors. Preclinical models suggested that ganetespib could be more active and have a better safety profile than the first-generation Hsp90 inhibitors. In phase I studies, ganetespib has demonstrated single-agent activity and has been well tolerated. Ganetespib appears to lack the dose-limiting hepatic and ocular toxicities observed with other Hsp90 inhibitors. The most common adverse event associated with ganetespib is diarrhea, which has been generally mild to moderate in severity and could be managed with supportive care.

To further evaluate the efficacy and safety of ganetespib in NSCLC, Wong and colleagues evaluated the agent in patients with previously treated stage IIIB/IV disease who had documented disease progression at study entry.[5] A total of 96 patients were enrolled between December 2009 and May 2011. Patients received ganetespib 200 mg/m^2 once weekly for 3 weeks of every 4-week cycle, with treatment continued until disease progression. Patients had mutant EGFR (n=16), mutant KRAS (n=17), wild-type EGFR/wild-type KRAS (n=25), or adenocarcinoma only (n=37).

The most common adverse events were diarrhea, fatigue, nausea, and decreased appetite. All other adverse

events occurred in fewer than 30% of patients. Generally, adverse events were grade 1/2 in severity and manageable with supportive care. Drug-related serious adverse events, occurring in 1 patient each, included asthenia, atrial fibrillation, cardiac arrest, diarrhea, lipase elevation, renal failure, and vomiting. Five patients died during the study, 2 due to possibly drug-related events, which included renal failure and cardiac arrest.

For the 76 patients evaluable for response, the primary endpoint—PFS rate at 16 weeks—was 24.1%. The objective response rate was 5.3%, the disease control rate as assessed by CR plus PR plus stable disease of 8 weeks or longer was 54.0%, and the disease control rate as assessed by CR plus PR plus stable disease of 16 weeks or longer was 21.1%. At the time of data analysis, 19 patients remained on treatment.

Differences in sensitivity to single-agent ganetespib were noted according to genetic features. All durable objective responses occurred in patients with tumors with ALK rearrangements. Among 8 crizotinib-naïve patients with ALK-positive tumors, 7 patients (88%) showed disease control and 4 patients (50%) had objective responses. No mutations were found beyond the EGFR and KRAS mutations. EGFR gene amplification analysis, conducted in 13 samples, showed no amplification but high polysomy in 4 samples.

Based on the demonstrated activity and safety profile in this phase II study, ganetespib is being further evaluated in patients with previously treated NSCLC. An ongoing phase IIb/III trial is evaluating combination therapy with ganetespib and docetaxel in the second-line treatment of patients with advanced NSCLC. Investigators are also continuing to evaluate biomarkers to determine which patients might be best suited to ganetespib therapy.

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Commentary

Mark. A. Socinski, MD

Although not the most commonly diagnosed cancer, lung cancer continues to be the leading cause of cancer-related mortality in the United States, accounting for approximately 160,000 deaths this year.[1] The association between smoking and an increased risk of lung cancer has been known for quite some time[2]; however, the majority of lifetime smokers do not develop lung cancer, and it is estimated that approximately 25,000 Americans who are true never-smokers (<100 cigarettes in their lifetime) will develop lung cancer this year. Several decades ago, the term non–small-cell lung cancer (NSCLC) was coined to effectively distinguish a group of diseases from the less common entity of small cell lung cancer, where therapeutic paradigms and the choice of chemotherapy agents differ. The major subtypes of NSCLC include adenocarcinoma, squamous carcinoma, and large cell carcinoma. It is common nowadays to divide NSCLC into nonsquamous versus squamous subtypes because of toxicity and efficacy issues related to bevacizumab[3] and pemetrexed,[4] respectively. It is clear that although the use of histology has been an important advance in the recent decade, the real challenge is to characterize the molecular heterogeneity of lung cancer and leverage molecular targets as actionable therapeutic options for genotypically defined subpopulations.

This year's American Society of Clinical Oncology (ASCO) annual meeting saw real progress in advancing this initiative. Dr. Mark Kris reported the initial findings of the Lung Cancer Mutation Consortium (LCMC) whose objective was to genotype 1,000 patients with the diagnosis of adenocarcinoma of the lung focusing on 10 driver mutations.[5] At the ASCO presentation, results were reported on 516 patients. Interestingly, slightly more than half (54%) of the patients tested had a molecular abnormality that affected therapy or made a clinical trial examining a new targeted agent a viable option for the patient. The most commonly diagnosed molecular abnormality was the finding of a *KRAS* mutation, which defines a population of NSCLC patients that remain therapeutically challenging. Mutations in the epidermal growth factor receptor

(EGFR) gene and translocations in the EML4-ALK gene were found in 17% and 7% of patients, respectively. Other findings such as mutations in BRAF, HER2, PIK3CA, AKT1, NRAS, MEK1, and amplification of MET were found in a small percentage of patients. Only 3% of patients had more than 1 molecular abnormality defined (usually MET amplification and a PIK3CA mutation), suggesting that most of these findings are mutually exclusive. More information will be forthcoming from the LCMC as perhaps more cases are added and other molecular findings are evaluated. No information about the demographics of the patients included in the initial preliminary data was presented. Given the rate of EGFR mutations and EML4-ALK translocations, there may have been a slight bias regarding inclusion of never or former light smokers. This presentation is an incredibly important one, as it is the first large-scale attempt at molecular definition of adenocarcinoma of the lung in the era of targeted therapies.

The finding of an EGFR mutation has both prognostic and predictive implications. The EURTAC trial (presented by Dr. Raphael Rosell) randomized 173 advanced NSCLC patients who had either an exon 19 or 21 EGFR mutation to receive either erlotinib or platinum-based chemotherapy.[6] The primary endpoint was progression-free survival (PFS). There was a significant improvement in PFS with erlotinib compared to chemotherapy (hazard ratio [HR], 0.42; $P<.0001$). No survival advantage was seen, which is likely explained by the fact that nearly all of the mutation-positive patients randomized to chemotherapy received erlotinib upon progression. This trial follows at least 5 previous phase III reports[7-11] comparing an EGFR tyrosine kinase inhibitor (TKI) to chemotherapy in either clinically- or molecularly-defined mutation-enriched populations, and reinforced the message from all of these trials that an EGFR TKI is superior to chemotherapy in patients with an EGFR mutation. This superiority is measured not only by PFS but also by superior response rates, toxicity profiles, and quality of life. Although none of these trials have shown a survival difference likely due to a cross-over effect, the clinical benefit to the patient is overwhelmingly in favor of an EGFR TKI in my opinion. The importance of genotyping was also shown in the randomized, phase II INNOVATIONS trial comparing erlotinib plus bevacizumab to cisplatin/gemcitabine plus bevacizumab in unselected first-line advanced NSCLC patients.[12] In this predominantly EGFR wild-type patient population, the "targeted" approach using erlotinib plus bevacizumab was less effective than a standard platinum-based doublet plus bevacizumab, underscoring the importance of genotyping in deciding the optimal first-line approach.

At last year's ASCO meeting, the activity of crizotinib in advanced NSCLC patients harboring the EML4-ALK translocation was initially reported[13] and was as impressive as the activity of the EGFR TKIs in patients with EGFR mutations. Dr. Crinò and colleagues[14] confirmed these findings in a preliminary report of PROFILE1005, which is a phase II trial of crizotinib in EML4-ALK translocated advanced NSCLC patients. Dr. Shaw presented an insightful analysis of the impact of crizotinib on survival in this unique population. It would be unethical in my opinion to conduct a trial where EML4-ALK-positive patients would be randomized to either an ALK inhibitor versus a placebo. Dr. Shaw and colleagues[15] compared survival outcomes in EML4-ALK-positive patients treated with crizotinib to EML4-ALK-positve patients who were crizotinib-naïve. This was not a randomized experience, but it strongly suggested a significant survival effect of crizotinib in this molecularly-defined population. Lee and colleagues[16] presented data suggesting that EML4-ALK-positive patients treated with an EGFR TKI may have a shortened PFS, which again underscores the importance of genotying. Both EGFR mutations and EML4-ALK translocations occur more commonly in light or never-smokers with adenocarcinoma. These patients cannot be reliably identified on clinical grounds alone. The historic practice of using an EGFR TKI based on clinical criteria is not optimal, as a never smoker who is EGFR-wild type and harbors an EML4-ALK translocation may be harmed (or at best not significantly helped) by an EGFR TKI.

Dr. Geoff Shapiro reported the results of a phase II trial of ganetespib (STA-9090) in advanced, refractory NSCLC.[17] Malignant cells rely on heat shock proteins (hsp) to preserve mutated and overexpressed oncoproteins. Historically, Hsp90 inhibition in lung cancer has been evaluated with first-generation drugs such as 17AAG and 17DMAG. These early trials did not show clinical activity and were plagued by significant hepatic toxicity. Ganetespib is a second-generation Hsp90 inhibitor, which is a more potent inhibitor of the Hsp90 complex. Ganetespib was evaluated in 3 distinct molecular cohorts based on the activity of this class of drugs in preclinical animal models: EGFR mutant, KRAS mutant, and EGFR/KRAS wild type. This phase II trial is important as it ushers in the era of Hsp90 therapy in a molecularly selected population. Activity of ganetespib worthy of cohort expansion was seen only in the EGFR/KRAS wild-type cohort. On further molecular analysis, it appears that objective responses were seen only in the EML4-ALK-positive patients. Many preclinical observations show that EML4-ALK is an Hsp90 client, inhibition of Hsp90 results in loss of ALK signaling, and Hsp90 inhibition can overcome crizotinib resistance. All of these observations provide a strong rationale for the continued development of ganetespib in EML4-ALK-positive patients. Fortunately, ganetespib was well tolerated without undue safety concerns. Diarrhea and fatigue were the most common toxici-

ties, most of which was grade 2 or less (only approximately 10% of patients had grade 3 diarrhea).

Bevacizumab is a monoclonal antibody to vascular endothelial growth factor (VEGF) and was shown by Sandler and colleagues[18] to improve survival when added to carboplatin/paclitaxel in advanced nonsquamous NSCLC. This pivotal trial established the role of anti-angiogenic therapy in lung cancer. Targeting the VEGF pathway with novel targeted agents has been the focus of many trials, 2 of which were reported at this year's ASCO meeting. Vadimezan (ASA404) is a small molecule vascular disrupting agent that in preclinical models leads to loss of integrity of tumor microvasculature, culminating in hemorrhagic tumor necrosis. Motesanib is a multi targeted small molecule inhibiting the VEGF receptors 1, 2, and 3, as well as platelet-derived growth factor (PDGF) receptors. Disappointingly, 2 phase III trials comparing the addition of vadimezan[19] or motesanib[20] to carboplatin/paclitaxel failed to show any benefit compared to carboplatin/paclitaxel alone. Bevacizumab remains the only anti-angiogenic agent with proven efficacy in advanced NSCLC in combination with chemotherapy. The impact of bevacizumab in the adjuvant setting is being explored in a randomized phase III trial being coordinated by the Eastern Cooperative Oncology Group (ECOG 1505). Wakelee and colleagues reported on the interim safety evaluation of bevacizumab in this setting, in which patients with resected stage IB (>4 cm), II, and III NSCLC are randomized to cisplatin-based adjuvant chemotherapy with or without bevacizumab.[21] Although certain toxicities (hypertension, proteinuria, abdominal pain) were increased on the bevacizumab arm of ECOG 1505, there have been no unexpected toxicities, and there has been no difference in treatment-related death rates between the 2 arms. This is reassuring, but the increased rate of toxicity must be offset by a clinically meaningful benefit in survival.

The role of pemetrexed as switch maintenance was defined by Ciuleanu and colleagues[22] in a placebo-controlled randomized phase III trial. This year's ASCO meeting saw the initial preliminary presentation of the PARAMOUNT trial,[23] which evaluated pemetrexed as continuation maintenance following 4 cycles of first-line cisplatin/pemetrexed. The primary endpoint was PFS. Continuation maintenance with pemetrexed resulted in a significant improvement in PFS (HR, 0.62; $P<.00006$). This trial reinforced the common practice of continuation pemetrexed maintenance in the United States, given the frequent use of pemetrexed in combination with platinum in the first-line setting. The INFORM trial[24] evaluated gefitinib as maintenance therapy following 4 cycles of first-line therapy with a platinum-based doublet. This trial was performed by the Chinese Thoracic Oncology Group and essentially confirmed the results seen with erlotinib in the SATURN trial.[25] As expected, the INFORM study had a relatively high percentage of patients with EGFR mutations, and the benefit with gefitinib as maintenance in these patients was quite impressive (HR, 0.17; 95% confidence interval, 0.07–0.42).

In summary, we have entered a new era in the management of advanced NSCLC. Sufficient sampling for tumors should be routine, allowing for the optimal assessment of histology; it is important to have adequate tissue available for genotyping in nearly all patients with this disease. Certainly the finding of either an EGFR mutation or an EML4-ALK translocation will change the therapeutic approach in these patients and lead to better outcomes using targeted therapies. The challenge lies in the molecular definition of and demonstration that new targeted agents directed at specific populations of advanced NSCLC will offer patients better therapies.

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AVASTIN® (bevacizumab)

Solution for intravenous infusion
Initial U.S. Approval: 2004

WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND HEALING COMPLICATIONS, and HEMORRHAGE

Gastrointestinal Perforations

The incidence of gastrointestinal perforation, some fatal, in Avastin-treated patients ranges from 0.3 to 2.4%. Discontinue Avastin in patients with gastrointestinal perforation. *[See Dosage and Administration (2.4), Warnings and Precautions (5.1).]*

Surgery and Wound Healing Complications

The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients. Discontinue Avastin in patients with wound dehiscence. The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined. Discontinue at least 28 days prior to elective surgery. Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. *[See Dosage and Administration (2.4), Warnings and Precautions (5.2), and Adverse Reactions (6.1).]*

Hemorrhage

Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, central nervous systems (CNS) hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis. *[See Dosage and Administration (2.4), Warnings and Precautions (5.3), and Adverse Reactions (6.1).]*

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer (mCRC)

Avastin is indicated for the first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil–based chemotherapy.

1.2 Non-Squamous Non–Small Cell Lung Cancer (NSCLC)

Avastin is indicated for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer in combination with carboplatin and paclitaxel.

1.3 Metastatic Breast Cancer (MBC)

Avastin is indicated for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer in combination with paclitaxel.

The effectiveness of Avastin in MBC is based on an improvement in progression free survival. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin. *[See Clinical Studies (14.3).]*

Avastin is not indicated for patients with breast cancer that has progressed following anthracycline and taxane chemotherapy administered for metastatic disease.

1.4 Glioblastoma

Avastin is indicated for the treatment of glioblastoma with progressive disease in adult patients following prior therapy as a single agent.

The effectiveness of Avastin in glioblastoma is based on an improvement in objective response rate. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin. *[See Clinical Studies (14.4).]*

1.5 Metastatic Renal Cell Carcinoma (mRCC)

Avastin is indicated for the treatment of metastatic renal cell carcinoma in combination with interferon alfa.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Perforations

Serious and sometimes fatal gastrointestinal perforation occurs at a higher incidence in Avastin treated patients compared to controls. The incidence of gastrointestinal perforation ranged from 0.3 to 2.4% across clinical studies. *[See Adverse Reactions (6.1).]*

The typical presentation may include abdominal pain, nausea, emesis, constipation, and fever. Perforation can be complicated by intra-abdominal abscess and fistula formation. The majority of cases occurred within the first 50 days of initiation of Avastin.

Discontinue Avastin in patients with gastrointestinal perforation. *[See Boxed Warning, Dosage and Administration (2.4).]*

5.2 Surgery and Wound Healing Complications

Avastin impairs wound healing in animal models. *[See Nonclinical Toxicology (13.2).]* In clinical trials, administration of Avastin was not allowed until at least 28 days after surgery. In a controlled clinical trial, the incidence of wound healing complications, including serious and fatal complications, in patients with mCRC who underwent surgery during the course of Avastin treatment was 15% and in patients who did not receive Avastin, was 4%. *[See Adverse Reactions (6.1).]*

Avastin should not be initiated for at least 28 days following surgery and until the surgical wound is fully healed. Discontinue Avastin in patients with wound healing complications requiring medical intervention.

The appropriate interval between the last dose of Avastin and elective surgery is unknown; however, the half-life of Avastin is estimated to be 20 days. Suspend Avastin for at least 28 days prior to elective surgery. Do not administer Avastin until the wound is fully healed. *[See Boxed Warning, Dosage and Administration (2.4).]*

5.3 Hemorrhage

Avastin can result in two distinct patterns of bleeding: minor hemorrhage, most commonly Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal

hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin compared to patients receiving only chemotherapy. Across indications, the incidence of Grade ≥ 3 hemorrhagic events among patients receiving Avastin ranged from 1.2 to 4.6%. *[See Adverse Reactions (6.1).]*

Serious or fatal pulmonary hemorrhage occurred in four of 13 (31%) patients with squamous cell histology and two of 53 (4%) patients with non-squamous non-small cell lung cancer receiving Avastin and chemotherapy compared to none of the 32 (0%) patients receiving chemotherapy alone.

In clinical studies in non–small cell lung cancer where patients with CNS metastases who completed radiation and surgery more than 4 weeks prior to the start of Avastin were evaluated with serial CNS imaging, symptomatic Grade 2 CNS hemorrhage was documented in one of 83 Avastin-treated patients (rate 1.2%, 95% CI 0.06%–5.93%).

Intracranial hemorrhage occurred in 8 of 163 patients with previously treated glioblastoma; two patients had Grade 3–4 hemorrhage.

Do not administer Avastin to patients with recent history of hemoptysis of ≥1/2 teaspoon of red blood. Discontinue Avastin in patients with hemorrhage. *[See Boxed Warning, Dosage and Administration (2.4).]*

5.4 Non-Gastrointestinal Fistula Formation

Serious and sometimes fatal non-gastrointestinal fistula formation involving tracheo-esophageal, bronchopleural, biliary, vaginal, renal and bladder sites occurs at a higher incidence in Avastin-treated patients compared to controls. The incidence of non-gastrointestinal perforation was ≤0.3% in clinical studies. Most events occurred within the first 6 months of Avastin therapy.

Discontinue Avastin in patients with fistula formation involving an internal organ. *[See Dosage and Administration (2.4).]*

5.5 Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a higher incidence in patients receiving Avastin compared to those in the control arm. Across indications, the incidence of Grade ≥ 3 ATE in the Avastin containing arms was 2.4% compared to 0.7% in the control arms. Among patients receiving Avastin in combination with chemotherapy, the risk of developing ATE during therapy was increased in patients with a history of arterial thromboembolism, or age greater than 65 years. *[See Use in Specific Populations (8.5).]*

The safety of resumption of Avastin therapy after resolution of an ATE has not been studied. Discontinue Avastin in patients who experience a severe ATE. *[See Dosage and Administration (2.4).]*

5.6 Hypertension

The incidence of severe hypertension is increased in patients receiving Avastin as compared to controls. Across clinical studies the incidence of Grade 3 or 4 hypertension ranged from 5-18%.

Monitor blood pressure every two to three weeks during treatment with Avastin. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. Continue to monitor blood pressure at regular intervals in patients with Avastin-induced or -exacerbated hypertension after discontinuation of Avastin.

Temporarily suspend Avastin in patients with severe hypertension that is not controlled with medical management. Discontinue Avastin in patients with hypertensive crisis or hypertensive encephalopathy. *[See Dosage and Administration (2.4).]*

5.7 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

RPLS has been reported with an incidence of <0.1% in clinical studies. The onset of symptoms occurred from 16 hours to 1 year after initiation of Avastin. RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging (MRI) is necessary to confirm the diagnosis of RPLS.

Discontinue Avastin in patients developing RPLS. Symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae. The safety of reinitiating Avastin therapy in patients previously experiencing RPLS is not known. *[See Dosage and Administration (2.4).]*

5.8 Proteinuria

The incidence and severity of proteinuria is increased in patients receiving Avastin as compared to controls. Nephrotic syndrome occurred in < 1% of patients receiving Avastin in clinical trials, in some instances with fatal outcome. *[See Adverse Reactions (6.1).]* In a published case series, kidney biopsy of six patients with proteinuria showed findings consistent with thrombotic microangiopathy.

Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during Avastin therapy. Patients with a 2 + or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection.

Suspend Avastin administration for ≥ 2 grams of proteinuria/24 hours and resume when proteinuria is <2 gm/24 hours. Discontinue Avastin in patients with nephrotic syndrome. Data from a postmarketing safety study showed poor correlation between UPCR (Urine Protein/Creatinine Ratio) and 24 hour urine protein (Pearson Correlation 0.39 (95% CI 0.17, 0.57). *[See Use in Specific Populations (8.5).]* The safety of continued Avastin treatment in patients with moderate to severe proteinuria has not been evaluated. *[See Dosage and Administration (2.4).]*

5.9 Infusion Reactions

Infusion reactions reported in the clinical trials and post-marketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. In clinical studies, infusion reactions with the first dose of Avastin were uncommon (< 3%) and severe reactions occurred in 0.2% of patients.

Stop infusion if a severe infusion reaction occurs and administer appropriate medical therapy. *[See Dosage and Administration (2.4).]*

AVASTIN® (bevacizumab)

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Gastrointestinal Perforations *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.1).]*
- Surgery and Wound Healing Complications *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.2).]*
- Hemorrhage *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.3).]*
- Non-Gastrointestinal Fistula Formation *[See Dosage and Administration (2.4), Warnings and Precautions (5.4).]*
- Arterial Thromboembolic Events *[See Dosage and Administration (2.4), Warnings and Precautions (5.5).]*
- Hypertensive Crisis *[See Dosage and Administration (2.4), Warnings and Precautions (5.6).]*
- Reversible Posterior Leukoencephalopathy Syndrome *[See Dosage and Administration (2.4), Warnings and Precautions (5.7).]*
- Proteinuria *[See Dosage and Administration (2.4), Warnings and Precautions (5.8).]*

The most common adverse reactions observed in Avastin patients at a rate > 10% and at least twice the control arm rate, are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis.

Across all studies, Avastin was discontinued in 8.4 to 21% of patients because of adverse reactions.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data below reflect exposure to Avastin in 2661 patients with mCRC, non-squamous NSCLC, MBC, glioblastoma, or mRCC in controlled (Studies 1, 2, 4, 5, 6 and 9) or uncontrolled, single arm (Study 7) trials treated at the recommended dose and schedule for a median of 8 to 16 doses of Avastin. *[See Clinical Studies (14).]* The population was aged 21-88 years (median 59), 46.0% male and 84.1% white. The population included 1089 first- and second-line mCRC patients who received a median of 11 doses of Avastin, 480 first-line metastatic NSCLC patients who received a median of 8 doses of Avastin, 592 MBC patients who had not received chemotherapy for metastatic disease received a median of 8 doses of Avastin, 163 glioblastoma patients who received a median of 9 doses of Avastin, and 337 mRCC patients who received a median of 16 doses of Avastin.

Surgery and Wound Healing Complications

The incidence of post-operative wound healing and/or bleeding complications was increased in patients with mCRC receiving Avastin as compared to patients receiving only chemotherapy. Among patients requiring surgery on or within 60 days of receiving study treatment, wound healing and/or bleeding complications occurred in 15% (6/39) of patients receiving bolus-IFL plus Avastin as compared to 4% (1/25) of patients who received bolus-IFL alone.

In Study 7, events of post-operative wound healing complications (craniotomy site wound dehiscence and cerebrospinal fluid leak) occurred in patients with previously treated glioblastoma: 3/84 patients in the Avastin alone arm and 1/79 patients in the Avastin plus irinotecan arm. *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.2).]*

Hemorrhage

The incidence of epistaxis was higher (35% vs. 10%) in patients with mCRC receiving bolus-IFL plus Avastin compared with patients receiving bolus-IFL plus placebo. All but one of these events were Grade 1 in severity and resolved without medical intervention. Grade 1 or 2 hemorrhagic events were more frequent in patients receiving bolus-IFL plus Avastin when compared to those receiving bolus-IFL plus placebo and included gastrointestinal hemorrhage (24% vs. 6%), minor gum bleeding (2% vs. 0), and vaginal hemorrhage (4% vs. 2%). *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.3).]*

Venous Thromboembolic Events

The incidence of Grade 3–4 venous thromboembolic events was higher in patients with mCRC or NSCLC receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone. The risk of developing a second subsequent thromboembolic event in mCRC patients receiving Avastin and chemotherapy was increased compared to patients receiving chemotherapy alone. In Study 1, 53 patients (14%) on the bolus-IFL plus Avastin arm and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose warfarin following a venous thromboembolic event. Among these patients, an additional thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus Avastin and 3% (1/30) of patients receiving bolus-IFL alone.

The overall incidence of Grade 3–4 venous thromboembolic events in Study 1 was 15.1% in patients receiving bolus-IFL plus Avastin and 13.6% in patients receiving bolus-IFL plus placebo. In Study 1, the incidence of the following Grade 3–4 venous thromboembolic events was higher in patients receiving bolus-IFL plus Avastin as compared to patients receiving bolus-IFL plus placebo: deep venous thrombosis (34 vs. 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

Neutropenia and Infection

The incidences of neutropenia and febrile neutropenia are increased in patients receiving Avastin plus chemotherapy compared to chemotherapy alone. In Study 1, the incidence of Grade 3 or 4 neutropenia was increased in mCRC patients receiving IFL plus Avastin (21%) compared to patients receiving IFL alone (14%). In Study 4, the incidence of Grade 4 neutropenia was increased in NSCLC patients receiving paclitaxel/carboplatin (PC) plus Avastin (26.2%) compared with patients receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus Avastin vs. 1.8% for PC alone). There were 19 (4.5%) infections with Grade 3 or 4 neutropenia in the PC plus Avastin arm of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving PC alone, of which none were fatal. During the first 6 cycles of treatment, the incidence of serious infections including pneumonia, febrile neutropenia, catheter infections and wound infections was increased in the PC plus Avastin arm [58 patients (13.6%)] compared to the PC alone arm [29 patients (6.6%)].

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In Study 7, one fatal event of neutropenic infection occurred in a patient with previously treated glioblastoma receiving Avastin alone. The incidence of any grade of infection in patients receiving Avastin alone was 55% and the incidence of Grade 3-5 infection was 10%.

Proteinuria

Grade 3-4 proteinuria ranged from 0.7 to 7.4% in Studies 1, 2, 4 and 9. The overall incidence of proteinuria (all grades) was only adequately assessed in Study 9, in which the incidence was 20%. Median onset of proteinuria was 5.6 months (range 15 days to 37 months) after initiation of Avastin. Median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months). Proteinuria did not resolve in 40% of patients after median follow up of 11.2 months and required permanent discontinuation of Avastin in 30% of the patients who developed proteinuria (Study 9). *[See Warnings and Precautions (5.8).]*

Congestive Heart Failure

The incidence of Grade ≥ 3 left ventricular dysfunction was 1.0% in patients receiving Avastin compared to 0.6% in the control arm across indications. In patients with MBC, the incidence of Grade 3-4 congestive heart failure (CHF) was increased in patients in the Avastin plus paclitaxel arm (2.2%) as compared to the control arm (0.3%). Among patients receiving prior anthracyclines for MBC, the rate of CHF was 3.8% for patients receiving Avastin as compared to 0.6% for patients receiving paclitaxel alone. The safety of continuation or resumption of Avastin in patients with cardiac dysfunction has not been studied.

Metastatic Colorectal Cancer (mCRC)

The data in Table 1 and Table 2 were obtained in Study 1, a randomized, double-blind, controlled trial comparing chemotherapy plus Avastin with chemotherapy plus placebo. Avastin was administered at 5 mg/kg every 2 weeks.

All Grade 3–4 adverse events and selected Grade 1–2 adverse events (hypertension, proteinuria, thromboembolic events) were collected in the entire study population. Severe and life-threatening (Grade 3–4) adverse events, which occurred at a higher incidence (≥ 2%) in patients receiving bolus-IFL plus Avastin as compared to bolus-IFL plus placebo, are presented in Table 1.

Table 1
NCI-CTC Grade 3–4 Adverse Events in Study 1
(Occurring at Higher Incidence [≥ 2%] Avastin vs. Control)

	Arm 1 IFL + Placebo (n = 396)	Arm 2 IFL + Avastin (n = 392)
NCI-CTC Grade 3-4 Events	74%	87%
Body as a Whole		
Asthenia	7%	10%
Abdominal Pain	5%	8%
Pain	5%	8%
Cardiovascular		
Hypertension	2%	12%
Deep Vein Thrombosis	5%	9%
Intra-Abdominal Thrombosis	1%	3%
Syncope	1%	3%
Digestive		
Diarrhea	25%	34%
Constipation	2%	4%
Hemic/Lymphatic		
Leukopenia	31%	37%
Neutropenia[a]	14%	21%

[a]Central laboratories were collected on Days 1 and 21 of each cycle. Neutrophil counts are available in 303 patients in Arm 1 and 276 in Arm 2.

Grade 1–4 adverse events which occurred at a higher incidence (≥ 5%) in patients receiving bolus-IFL plus Avastin as compared to the bolus-IFL plus placebo arm are presented in Table 2. Grade 1–4 adverse events were collected for the first approximately 100 patients in each of the three treatment arms who were enrolled until enrollment in Arm 3 (5-FU/LV + Avastin) was discontinued.

Table 2
NCI-CTC Grade 1-4 Adverse Events in Study 1
(Occurring at Higher Incidence [≥ 5%] in IFL + Avastin vs. IFL)

	Arm 1 IFL + Placebo (n = 98)	Arm 2 IFL + Avastin (n = 102)	Arm 3 5-FU/LV + Avastin (n = 109)
Body as a Whole			
Pain	55%	61%	62%
Abdominal Pain	55%	61%	50%
Headache	19%	26%	26%
Cardiovascular			
Hypertension	14%	23%	34%
Hypotension	7%	15%	7%
Deep Vein Thrombosis	3%	9%	6%
Digestive			
Vomiting	47%	52%	47%
Anorexia	30%	43%	35%
Constipation	29%	40%	29%
Stomatitis	18%	32%	30%
Dyspepsia	15%	24%	17%
GI Hemorrhage	6%	24%	19%
Weight Loss	10%	15%	16%
Dry Mouth	2%	7%	4%
Colitis	1%	6%	1%
Hemic/Lymphatic			
Thrombocytopenia	0%	5%	5%
Nervous			
Dizziness	20%	26%	19%
Respiratory			
Upper Respiratory Infection	39%	47%	40%
Epistaxis	10%	35%	32%
Dyspnea	15%	26%	25%
Voice Alteration	2%	9%	6%
Skin/Appendages			
Alopecia	26%	32%	6%
Skin Ulcer	1%	6%	6%
Special Senses			
Taste Disorder	9%	14%	21%
Urogenital			
Proteinuria	24%	36%	36%

Avastin in Combination with FOLFOX4 in Second-line mCRC

Only Grade 3-5 non-hematologic and Grade 4–5 hematologic adverse events related to treatment were collected in Study 2. The most frequent adverse events (selected Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events) occurring at a higher incidence (≥ 2%) in 287 patients receiving FOLFOX4 plus Avastin compared to 285 patients receiving FOLFOX4 alone were fatigue (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%), vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8% vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache (3% vs. 0%). These data are likely to under-estimate the true adverse event rates due to the reporting mechanisms used in Study 2.

Unresectable Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in Study 4. Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events (occurring at a higher incidence (≥2%) in 427 patients receiving PC plus Avastin compared with 441 patients receiving PC alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs. 0.7%), infection without neutropenia (7% vs. 3%), venous thrombus/embolism (5% vs. 3%), febrile neutropenia (5% vs. 2%), pneumonitis/pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3% vs. 0%).

Metastatic Breast Cancer (MBC)

Only Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events were collected in Study 5. Grade 3–4 adverse events occurring at a higher incidence (≥2%) in 363 patients receiving paclitaxel plus Avastin compared with 348 patients receiving paclitaxel alone were sensory neuropathy (24% vs. 18%), hypertension (16% vs. 1%), fatigue (11% vs. 5%), infection without neutropenia (9% vs. 5%), neutrophils (6% vs. 3%), vomiting (6% vs. 2%), diarrhea (5% vs. 1%), bone pain (4% vs. 2%), headache (4% vs. 1%), nausea (4% vs. 1%), cerebrovascular ischemia (3% vs. 0%), dehydration (3% vs. 1%), infection with unknown ANC (3% vs. 0.3%), rash/desquamation (3% vs. 0.3%) and proteinuria (3% vs. 0%).

Sensory neuropathy, hypertension, and fatigue were reported at a ≥ 5% higher absolute incidence in the paclitaxel plus Avastin arm compared with the paclitaxel alone arm.

Fatal adverse reactions occurred in 6/363 (1.7%) of patients who received paclitaxel plus Avastin. Causes of death were gastrointestinal perforation (2), myocardial infarction (2), diarrhea/abdominal, and pain/weakness/hypotension (2).

Avastin is not approved for use in combination with capecitabine or for use in second or third line treatment of MBC. The data below are presented to provide information on the overall safety profile of Avastin in women with breast cancer since Study 6 is the only randomized, controlled study in which all adverse events were collected for all patients. All patients in Study 6 received prior anthracycline and taxane therapy in the adjuvant setting or for metastatic disease. Grade 1– 4 events which occurred at a higher incidence (≥5%) in patients receiving capecitabine plus Avastin compared to the capecitabine alone arm are presented in Table 3.

Table 3
NCI-CTC Grade 1–4 Adverse Events in Study 6 (Occurring at Higher Incidence [≥5%] in Capecitabine + Avastin vs. Capecitabine Alone)

	Capecitabine (n = 215)	Capecitabine + Avastin (n = 229)
Body as a Whole		
Asthenia	47%	57%
Headache	13%	33%
Pain	25%	31%
Cardiovascular		
Hypertension	2%	24%
Digestive		
Stomatitis	19%	25%
Metabolic/Nutrition		
Weight loss	4%	9%
Musculoskeletal		
Myalgia	8%	14%
Respiratory		
Dyspnea	18%	27%
Epistaxis	1%	16%
Skin/Appendages		
Exfoliative dermatitis	75%	84%
Urogenital		
Albuminuria	7%	22%

Glioblastoma

All adverse events were collected in 163 patients enrolled in Study 7 who either received Avastin alone or Avastin plus irinotecan. All patients received prior radiotherapy and temozolomide. Avastin was administered at 10 mg/kg every 2 weeks alone or in combination with irinotecan. Avastin was discontinued due to adverse events in 4.8% of patients treated with Avastin alone.

In patients receiving Avastin alone (N=84), the most frequently reported adverse events of any grade were infection (55%), fatigue (45%), headache (37%), hypertension (30%), epistaxis (19%) and diarrhea (21%). Of these, the incidence of Grade ≥3 adverse events was infection (10%), fatigue (4%), headache (4%), hypertension (8%) and diarrhea (1%). Two deaths on study were possibly related to Avastin: one retroperitoneal hemorrhage and one neutropenic infection.

In patients receiving Avastin alone or Avastin plus irinotecan (N=163), the incidence of Avastin-related adverse events (Grade 1–4) were bleeding/hemorrhage (40%), epistaxis (26%), CNS hemorrhage (5%), hypertension (32%), venous thromboembolic event (8%), arterial thromboembolic event (6%), wound-healing complications (6%), proteinuria (4%), gastrointestinal perforation (2%), and RPLS (1%). The incidence of Grade 3–5 events in these 163 patients were bleeding/hemorrhage (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial thromboembolic event (3%), wound-healing complications (3%), proteinuria (1%), and gastrointestinal perforation (2%).

Metastatic Renal Cell Carcinoma (mRCC)

All grade adverse events were collected in Study 9. Grade 3–5 adverse events occurring at a higher incidence (≥ 2%) in 337 patients receiving interferon alfa (IFN-α) plus Avastin compared to 304 patients receiving IFN-α plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%), proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis), and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, haemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma).

Grade 1–5 adverse events occurring at a higher incidence (≥ 5%) in patients receiving IFN-α plus Avastin compared to the IFN-α plus placebo arm are presented in Table 4.

Table 4
NCI-CTC Grades 1–5 Adverse Events in Study 9
(Occuring at Higher Incidence [≥ 5%] in IFN-α + Avastin vs. IFN-α + Placebo)

System Organ Class/ Preferred term[a]	IFN-α + Placebo (n = 304)	IFN-α + Avastin (n = 337)
Gastrointestinal disorders		
Diarrhea	16%	21%
General disorders and administration site conditions		
Fatigue	27%	33%
Investigations		
Weight decreased	15%	20%
Metabolism and nutrition disorders		
Anorexia	31%	36%
Musculoskeletal and connective tissue disorders		
Myalgia	14%	19%
Back pain	6%	12%
Nervous system disorders		
Headache	16%	24%
Renal and urinary disorders		
Proteinuria	3%	20%
Respiratory, thoracic and mediastinal disorders		
Epistaxis	4%	27%
Dysphonia	0%	5%
Vascular disorders		
Hypertension	9%	28%

[a]Adverse events were encoded using MedDRA, Version 10.1.

The following adverse events were reported at a 5-fold greater incidence in the IFN-α plus Avastin arm compared to IFN-α alone and not represented in Table 4: gingival bleeding (13 patients vs. 1 patient); rhinitis (9 vs.0); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux disease (8 vs.1); tinnitus (7 vs. 1); tooth abscess (7 vs.0); mouth ulceration (6 vs. 0); acne (5 vs. 0); deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Avastin has not been adequately determined because the assay sensitivity was inadequate to reliably detect lower titers. Enzyme-linked immunosorbent assays (ELISAs) were performed on sera from approximately 500 patients treated with Avastin, primarily in combination with chemotherapy. High titer human anti-Avastin antibodies were not detected.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Avastin with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Avastin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: Polyserositis

Cardiovascular: Pulmonary hypertension, RPLS, Mesenteric venous occlusion

Eye disorders (reported from unapproved use for treatment of various ocular disorders): Endophthalmitis; Intraocular inflammation such as iritis and vitritis; Retinal detachment; Other retinal disorders; Increased intraocular pressure; Hemorrhage following intraocular injection including conjunctival, vitreous hemorrhage or retinal hemorrhage; Vitreous floaters; Visual disturbances; Ocular hyperemia; Ocular pain and/or discomfort

Gastrointestinal: Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration

Hemic and lymphatic: Pancytopenia

Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)

Respiratory: Nasal septum perforation, dysphonia

7 DRUG INTERACTIONS

A drug interaction study was performed in which irinotecan was administered as part of the FOLFIRI regimen with or without Avastin. The results demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan or its active metabolite SN38.

In a randomized study in 99 patients with NSCLC, based on limited data, there did not appear to be a difference in the mean exposure of either carboplatin or paclitaxel when each was administered alone or in combination with Avastin. However, 3 of the 8 patients receiving Avastin plus paclitaxel/carboplatin had substantially lower paclitaxel exposure after four cycles of treatment (at Day 63) than those at Day 0, while patients receiving paclitaxel/carboplatin without Avastin had a greater paclitaxel exposure at Day 63 than at Day 0.

In Study 9, there was no difference in the mean exposure of interferon alfa administered in combination with Avastin when compared to interferon alfa alone.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no studies of bevacizumab in pregnant women. Reproduction studies in rabbits treated with approximately 1 to 12 times the recommended human dose of bevacizumab resulted in teratogenicity, including an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested. Other observed effects included decreases in maternal and fetal body weights and an increased number of fetal resorptions. *[See Nonclinical Toxicology (13.3).]*

Human IgG is known to cross the placental barrier; therefore, bevacizumab may be transmitted from the mother to the developing fetus, and has the potential to cause fetal harm when administered to pregnant women. Because of the observed teratogenic effects of known inhibitors of angiogenesis in humans, bevacizumab should be used during pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus.

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8.3 Nursing Mothers

It is not known whether Avastin is secreted in human milk, but human IgG is excreted in human milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from bevacizumab, a decision should be made whether to discontinue nursing or discontinue drug, taking into account the half-life of the bevacizumab (approximately 20 days [range 11–50 days]) and the importance of the drug to the mother. *[See Clinical Pharmacology (12.3).]*

8.4 Pediatric Use

The safety, effectiveness and pharmacokinetic profile of Avastin in pediatric patients have not been established.

Antitumor activity was not observed among eight children with relapsed glioblastoma treated with bevacizumab and irinotecan. There is insufficient information to determine the safety and efficacy of Avastin in children with glioblastoma.

Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure). The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon cessation of treatment.

8.5 Geriatric Use

In Study 1, severe adverse events that occurred at a higher incidence (≥ 2%) in patients aged ≥65 years as compared to younger patients were asthenia, sepsis, deep thrombophlebitis, hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation, anorexia, leukopenia, anemia, dehydration, hypokalemia, and hyponatremia. The effect of Avastin on overall survival was similar in elderly patients as compared to younger patients.

In Study 2, patients aged ≥ 65 years receiving Avastin plus FOLFOX4 had a greater relative risk as compared to younger patients for the following adverse events: nausea, emesis, ileus, and fatigue.

In Study 4, patients aged ≥ 65 years receiving carboplatin, paclitaxel, and Avastin had a greater relative risk for proteinuria as compared to younger patients. *[See Warnings and Precautions (5.8).]*

In Study 5, there were insufficient numbers of patients ≥ 65 years old to determine whether the overall adverse events profile was different in the elderly as compared with younger patients.

Of the 742 patients enrolled in Genentech-sponsored clinical studies in which all adverse events were captured, 212 (29%) were age 65 or older and 43 (6%) were age 75 or older. Adverse events of any severity that occurred at a higher incidence in the elderly as compared to younger patients, in addition to those described above, were dyspepsia, gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice alteration.

In an exploratory, pooled analysis of 1745 patients treated in five randomized, controlled studies, there were 618 (35%) patients aged ≥65 years and 1127 patients <65 years of age. The overall incidence of arterial thromboembolic events was increased in all patients receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone, regardless of age. However, the increase in arterial thromboembolic events incidence was greater in patients aged ≥ 65 years (8.5% vs. 2.9%) as compared to those < 65 years (2.1% vs. 1.4%). *[See Warnings and Precautions (5.5).]*

10 OVERDOSAGE

The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of 16 patients and with severe headache in three of 16 patients.

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Avastin® (bevacizumab)

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA
94080-4990

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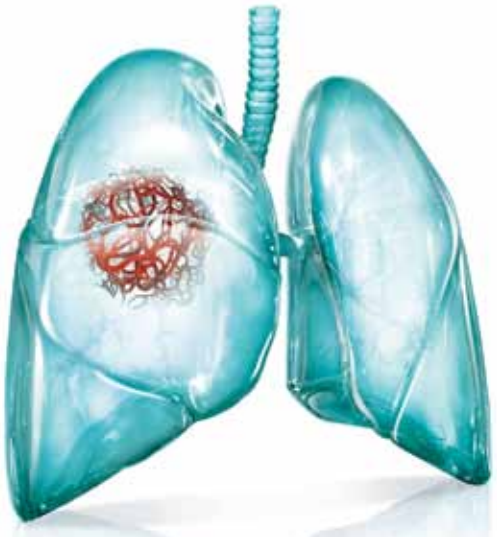
Initial U.S.Approval: February 2004
Code Revision Date: February 2011

To confront the threat of angiogenesis
in first-line metastatic non-squamous NSCLC…

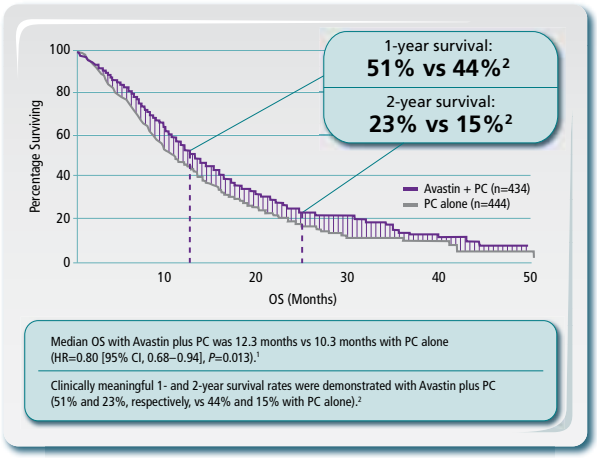
Think Avastin

Because survival matters most



NSCLC=non-small cell lung cancer; PC=paclitaxel/carboplatin; OS=overall survival; HR=hazard ratio; CI=confidence interval.

Avastin plus PC significantly increased median OS by 19% (12.3 vs 10.3 months with PC alone) in Study E4599[1]



Patients receiving Avastin plus PC vs PC alone were 16% more likely to be alive at 1 year (51% vs 44%) and 53% more likely to be alive at 2 years (23% vs 15%).[2]

Indication

Avastin is indicated for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer in combination with carboplatin and paclitaxel.

Boxed WARNINGS and additional important safety information

- **Gastrointestinal (GI) perforation:** Serious and sometimes fatal GI perforation occurs at a higher incidence in Avastin-treated patients compared to controls. The incidences of GI perforation ranged from 0.3% to 2.4% across clinical studies. Discontinue Avastin in patients with GI perforation
- **Surgery and wound healing complications:** The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients. Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined. Discontinue Avastin at least 28 days prior to elective surgery and in patients with wound dehiscence requiring medical intervention
- **Hemorrhage:** Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin. Across indications, the incidence of grade ≥3 hemorrhagic events among patients receiving Avastin ranged from 1.2% to 4.6%. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis (≥1/2 tsp of red blood). Discontinue Avastin in patients with serious hemorrhage (ie, requiring medical intervention)
- Additional serious and sometimes fatal adverse events for which the incidence was increased in the Avastin-treated arm vs control included non-GI fistula formation (≤0.3%), arterial thromboembolic events (grade ≥3, 2.4%), and proteinuria including nephrotic syndrome (<1%). Additional serious adverse events for which the incidence was increased in the Avastin-treated arm vs control included hypertension (grade 3–4, 5%–18%) and reversible posterior leukoencephalopathy syndrome (RPLS) (<0.1%). Infusion reactions with the first dose of Avastin were uncommon (<3%), and severe reactions occurred in 0.2% of patients
- The most common adverse reactions observed in Avastin patients at a rate >10% and at least twice the control arm rate were epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain, and exfoliative dermatitis. Across all studies, Avastin was discontinued in 8.4% to 21% of patients because of adverse reactions
- Based on animal data, Avastin may cause fetal harm and may impair fertility. Advise patients of the potential risk to the fetus during and following Avastin and the need to continue adequate contraception for at least 6 months following the last dose of Avastin. For nursing mothers, discontinue nursing or Avastin, taking into account the importance of Avastin to the mother
- Grade 3–5 (nonhematologic) and grade 4–5 (hematologic) adverse events in Study E4599 occurring at a ≥2% higher incidence in Avastin-treated patients vs controls were neutropenia (27% vs 17%), fatigue (16% vs 13%), hypertension (8% vs 0.7%), infection without neutropenia (7% vs 3%), venous thrombus/embolism (5% vs 3%), febrile neutropenia (5% vs 2%), pneumonitis/pulmonary infiltrates (5% vs 3%), infection with grade 3 or 4 neutropenia (4% vs 2%), hyponatremia (4% vs 1%), headache (3% vs 1%), and proteinuria (3% vs 0%)

Please see accompanying brief summary of Prescribing Information, including **Boxed WARNINGS**, for additional important safety information.

References: 1. Avastin Prescribing Information. Genentech, Inc. February 2011. **2.** Sandler A, Gray R, Perry MC, et al. *N Engl J Med.* 2006;355:2542-2550.

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