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Highlights in NSCLC From the IASLC 14th World Conference on Lung Cancer

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Special Reporting on:

- State of the Art Medical Treatment in 2011
- The PARAMOUNT Trial: Pemetrexed Maintenance Therapy
- The EURTAC Study: Erlotinib Versus Chemotherapy
- Bevacizumab and Erlotinib in Treatment-Naïve Elderly Patients
- ECOG 4599: Clinical Characteristics and Outcomes of the Maintenance Bevacizumab Population
- Crizotinib in ALK-Positive Patients
- ECOG E1505: Adjuvant Chemotherapy With or Without Bevacizumab for Completely Resected, Early Stage NSCLC

PLUS Meeting Abstract Summaries

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State of the Art Medical Treatment in 2011

Dr. David R. Gandara discussed advances in the management of advanced non–small cell lung cancer (NSCLC).[1] The standard of care for patients with advanced NSCLC and good performance status scores is platinum-based doublet chemotherapy for 4 to 6 cycles, followed by an option of continuation or switch to maintenance therapy. Several years ago, most selection factors were either clinical or histologic. Therefore, most patients were differentiated by performance status and squamous versus nonsquamous histology. The differentiation of histology was particularly important for therapies such as pemetrexed and bevacizumab, as patients with squamous NSCLC were excluded from these regimens. The treatment paradigm remains relatively the same in 2011, with the exception of the approval of crizotinib for ALK-fusion positive patients. Currently, there are 3 major components to consider when managing patients with advanced NSCLC: histology-based therapy, maintenance therapy, and predictive molecular biomarkers. These factors are interrelated and should not be considered independently.

NSCLC is a heterogeneous group of malignancies, including adenocarcinoma, squamous cell carcinoma, large cell carcinoma (neuroendocrine and non-neuroendocrine), and not otherwise specified (NOS). In the histologic distribution of NSCLC, 20% are classified as NOS. This presents a significant impediment to therapy. Although a small proportion of patients have truly undifferentiated cancers, the majority of those classified as NOS can be diagnosed through fine needle aspiration. In a study of 100 patients classified as NOS, fine needle aspiration followed by immunohistochemistry (IHC) was able to identify the majority of these samples as likely or probable adenocarcinoma or squamous NSCLC, thus reducing the incidence of NOS in this study from 36% to 14%.[2] This study demonstrates that histology can be established in most patients with increased tissue sampling.

Randomized clinical trials suggest that histologic subtyping can be used as a chemotherapy selection factor. Based upon observations of differential efficacy of pemetrexed in squamous versus nonsquamous subtypes of NSCLC, it has been proposed that treatment of advanced NSCLC should be based upon histology. In a randomized trial from Dr. Gandara and colleagues, there was no difference in overall survival between cisplatin/pemetrexed and cisplatin/gemcitabine; however, cisplatin/pemetrexed was superior for the treatment of nonsquamous NSCLC but not squamous NSCLC.[3] The results of this study, along with retrospective analyses of other pemetrexed trials in NSCLC, led the US Food and Drug Administration (FDA) to restrict the use of pemetrexed to NSCLC patients with nonsquamous carcinoma.

The data demonstrating that histologic subtyping can dictate chemotherapy selection are primarily restricted to studies involving pemetrexed. The question then becomes: do these data apply to other chemotherapy drug classes? Dr. Gandara suggested that this observation is restricted to pemetrexed treatment. Although emerging evidence indicates that platinum-based chemotherapy agents may be more active in adenocarcinomas, there is high interpatient variability. Overall, histology is currently being used as a crude molecular selection device. Instead, Dr. Gandara suggests that clinicians move toward a true molecular profile for the identification and classification of carcinoma and its subsequent treatment.

After a patient undergoes 4–6 cycles of platinum-based therapy and has nonprogressive disease, a choice needs to be made regarding continuation maintenance versus switch maintenance, as well as when to start maintenance therapy. At the present time, if the patient is on bevacizumab

during induction, he or she will often receive bevacizumab as continuation maintenance. In the future, continuation maintenance may also include cetuximab and pemetrexed. In fact, the recent PARAMOUNT (Phase III Study of Maintenance Pemetrexed [Pem] Plus Best Supportive Care [BSC] Versus Placebo Plus BSC Immediately Following Induction Treatment With Pem Plus Cisplatin for Advanced Nonsquamous Non-Small Cell Lung Cancer) study by Paz-Ares and associates demonstrated a clinical benefit to continuation maintenance with pemetrexed.[4] For switch maintenance, there is a demonstrated benefit for pemetrexed after first-line therapy with a platinum plus non-pemetrexed regimen and for an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). It remains unclear when maintenance therapy should be administered; options include the point at which symptoms return, once there is chemotherapy scan progression, or a priori at the end of first-line therapy. Unfortunately, there is no simple answer that can be applied to all patients.

Future therapeutic decisions may be dictated by molecular biomarkers. Recent studies suggest that histology-based differences in clinical outcomes might be due to underlying molecular factors. The major question regarding molecular markers is how empiric data can be used to develop individualized therapy. This transition is complex. Selection of therapy that is molecular-based and individualized is predicated upon molecular profiling and biomarkers, which require adequate tumor tissue from each patient.

There are a number of potential predictive biomarkers. One biomarker that has been described for pemetrexed is thymidylate synthase, an enzyme that plays a role in DNA biosynthesis. In patients with NSCLC with lower thymidylate synthase expression levels, there is an increased likelihood of response to pemetrexed. However, there is a wide range of expression levels in individual patient tumors. ERCC1 and RRM1 may act as molecular selection factors for platinum compounds and/or gemcitabine, respectively. Cross-study results indicate that there is both a prognostic and predictive value associated with these molecular biomarkers; clinical trials are currently under way to validate these molecular biomarkers. A molecular biomarker that can be used to predict increased treatment efficacy of EGFR TKIs is EGFR mutation status; evidence suggests that EGFR mutation status predicts the activity of cetuximab in NSCLC. In addition, selective inhibitors of molecular targets are being developed. For example, crizotinib is a selective inhibitor of ALK-fusion gene-positive NSCLC. Currently, large-scale studies, such as the Collaborative Advanced Stage Tissue Lung Cancer (CASTLE) network study, are under way to collect tumor

ABSTRACT SUMMARY Preliminary results of a phase II study of metronomic chemotherapy (MC) with bevacizumab (B) in advanced (adv) non-small cell lung cancer (NSCLC)

Previous preclinical studies have shown that protracted, low-dose chemotherapy (metronomic chemotherapy) can control tumor growth and trigger apoptosis of tumor and endothelial cells. Robert and colleagues presented the preliminary results of a phase II study that aimed to determine if metronomic chemotherapy with gemcitabine and paclitaxel plus bevacizumab could achieve an improvement in progression-free survival (PFS) of 30% or more (compared to the 6.4-month PFS achieved in the Eastern Cooperative Oncology Group [ECOG] study 4599) in patients with advanced NSCLC (Abstract 515). The study also assessed safety, overall response rate (ORR), and overall survival, as well as the correlation between the kinetics of angiogenic biomarkers, hypertension, proteinuria, and tumor cavitation with clinical efficacy parameters. The study enrolled 29 chemotherapy-naïve, stage IIIb/IV, nonsquamous NSCLC patients (performance status 0–1, without active brain metastases). The median age of the patients was 57 years, 41% were male, and 76% were active or former heavy smokers. Patients received induction metronomic chemotherapy (weekly x 3, 4-week cycle) with paclitaxel (80 mg/m^2/week) plus gemcitabine (200–300 mg/m^2/week), and bevacizumab (10 mg/kg every 2 weeks) in a 4-week cycle. Patients received bevacizumab maintenance after completing 6 cycles of induction therapy. Of the 26 patients evaluable for response, an objective response was achieved in 72% (CR, 4%; PR, 68%; 19%, SD). The median PFS was 9 months; the median overall survival had not been reached. The authors of the study noted that the treatment was well tolerated; there were no incidences of significant grade 3 or 4 marrow suppression or gastrointestinal, neurologic, or constitutional adverse events. The majority of patients (approximately 70%) experienced increased blood pressure that was controlled with anti-hypertensive agents. Robert and associates concluded that metronomic chemotherapy plus bevacizumab was well tolerated in the treatment of patients with advanced NSCLC and warrants further investigation in a phase III study.

tissues, serum, and clinical data from advanced lung cancer patients in an effort to move molecular profiling forward. National database testing remains a viable option, as selective therapy for patients with defined molecular markers will become more commonplace.

Dr. Gandara concluded by stating that although progress is being made in the treatment and management of advanced NSCLC, it requires change. One necessary change is the collection of more tumor tissue samples. In addition, NSCLC needs to be ungrouped, and new drug development needs to account for the underlying biologic complexity, including interpatient and intrapatient heterogeneity.

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The PARAMOUNT Trial: Pemetrexed Maintenance Therapy

Many patients with NSCLC present with advanced or metastatic disease. The prognosis for these patients is often poor, with a median survival of 7 to 12 months.[1,2] For first-line therapy, current treatment guidelines recommend platinum-based combination regimens.[1] Newer approaches incorporate patient and disease characteristics, molecular-targeted therapies, and alterations in the treatment schedule, such as administration of maintenance chemotherapy after the induction phase.[3] This approach has the benefit of continuing successful chemotherapy while the tumor burden is low. In addition, if the same effective therapy used during the induction phase is sustained, patients can continue the chemotherapy with the favorable toxicity profile of a single-agent treatment.[3]

One agent that may be successful if continued into the maintenance phase is pemetrexed. Pemetrexed is an antifolate that has demonstrated efficacy in combination with cisplatin for the treatment of advanced nonsquamous NSCLC.[4] In addition, pemetrexed has demonstrated safety and efficacy as a maintenance therapy following non-pemetrexed containing platinum-based therapy; pemetrexed significantly improved overall survival and progression-free survival (PFS) in patients with NSCLC.[5] Therefore, Paz-Ares and associates sought to determine the safety and efficacy of pemetrexed as a maintenance therapy following induction therapy with pemetrexed plus cisplatin in patients with advanced nonsquamous NSCLC.[6] This double-blind, placebo-controlled, multicenter phase III study (PARAMOUNT) enrolled 939 treatment-naïve patients with advanced nonsquamous NSCLC and a good performance status. In the induction phase, patients received pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) on day 1 of a 21-day cycle for 4 cycles. If disease progressed, the patient went off protocol. Four hundred patients were ineligible for the maintenance phase due to disease progression, death, or adverse events. Patients who entered the maintenance phase had documented radiographic evidence of a tumor response indicating complete response (CR), partial response (PR), or stable disease (SD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. These patients were randomized 2:1 to receive pemetrexed (500 mg/m^2 on day 1 of a 21-day cycle) plus best supportive care (359 patients) or placebo plus best supportive care (180 patients) until disease progression. All patients received B_{12}, folic acid, and prophylactic dexamethasone. The primary endpoint was progression-free survival (PFS). Additional endpoints included overall survival, response rate (RR), and quality of life. PFS and disease control rate were independently reviewed.

The characteristics of patients entering the maintenance phase were unremarkable: the median age was 61 years, 58% were male, 95% were white, 32% had a performance status of 0, 91% had stage IV disease, 87% had adenocarcinoma, and 45% had complete/partial induction response. The mean number of treatment cycles was 4.9 in the pemetrexed arm (30.4% completed ≥6 cycles) and 4.2 cycles in the placebo arm (23.3% completed ≥6 cycles). At the time of the report, 38% of patients in the pemetrexed arm and 24% of patients in the placebo arm were still in treatment.

The study met its primary endpoint of PFS. There was a 36% reduction in the risk of progression for those patients in the pemetrexed continuation maintenance therapy arm (hazard ratio [HR], 0.64; 95% confidence interval [CI], 0.51–0.81; *P*=.00025), which Dr. Paz-Ares noted was clinically relevant. The median independently reviewed PFS (472 patients, 297 events) was 3.9 months for the patients in the pemetrexed arm (95% confidence interval [CI], 3.0–4.2) and 2.6 months for the patients in the placebo arm (95% CI, 2.2–2.9). Approximately 300 more events are required for the final analysis of survival. Patients in the pemetrexed arm had a better disease control rate, as measured by the percent of patients with response or stable disease, than patients in the placebo arm (71.8% vs 59.6%; *P*=.009; independently reviewed). Serious drug-related adverse events occurred in 8.9% of patients on pemetrexed and 2.8% of patients on placebo. Grade 3/4 common toxicity criteria adverse events occurred in 9.2% of patients on pemetrexed and 0.6% of patients on placebo. Treatment discontinuations due to adverse events occurred in 5.3% of the pemetrexed arm and 3.3% of the placebo arm.

The authors of the study concluded that pemetrexed maintenance therapy following pemetrexed-cisplatin induction was safe and effective for patients with advanced nonsquamous NSCLC. PFS was improved for patients treated with pemetrexed during maintenance therapy compared to patients treated with placebo. Dr. Paz-Ares further stated that these results are significant and clinically relevant, providing further support for the continued use of pemetrexed during maintenance therapy, even if the patient received pemetrexed during the induction phase. Furthermore, pemetrexed was well tolerated, with a comparable safety profile to single-agent pemetrexed for NSCLC.

ABSTRACT SUMMARY Sunitinib plus erlotinib for the treatment of advanced NSCLC: subset analysis of East Asian patients participating in a phase III trial

A recent double-blind phase III trial (SUN 1087) investigated the addition of sunitinib to erlotinib for the treatment of patients with NSCLC who failed prior chemotherapy. Although this study found that the addition of sunitinib significantly improved PFS and response rates, a significant improvement in overall survival was not observed. Because Asian patients may be more sensitive to antiangiogenic agents, Thongprasert and associates conducted a subset analysis of East Asian patients from the SUN 1087 trial (Abstract 1951). In the SUN 1087 trial, patients were stratified according to smoking history and prior treatment with bevacizumab. Patients (n=960) were randomized to receive sunitinib (37.5 mg/day) plus erlotinib (150 mg/day) or placebo plus erlotinib (150 mg/day; control group). The primary endpoint was overall survival. Among the East Asian patients (n=103), 67% were male, 40.8% were never smokers, 69.9% had nonsquamous histology, and 90.3% had stage IV disease. The ORR was 38.5% in the erlotinib plus sunitinib group and 13.7% in the control group (*P*=.0083). The addition of sunitinib to erlotinib increased the median overall survival (median not yet reached; 95% CI, 13.4–not reached) and resulted in 1 confirmed CR; the median overall survival of the control group was 9.4 months (95% CI, 7.2–15.4; *P*=.0042). The median PFS was 31.2 weeks in the sunitinib plus erlotinib group versus 15.2 weeks in the control group (HR, 0.723; 95% CI, 0.451–1.161; *P*=.0889). The most common nonhematologic adverse events were diarrhea and rash. There was 1 case of anemia in each arm of the study. The researchers concluded that adding sunitinib to erlotinib was associated with longer overall survival, improved ORR, and longer PFS in patients of East Asian descent. Although adverse events were more frequent in the sunitinib plus erlotinib treatment arm, East Asian patients with NSCLC may benefit from this combination regimen.

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The EURTAC Study: Erlotinib Versus Chemotherapy

Activation of EGFR initiates a complex signaling cascade that plays a role in accelerated cell growth and the development of cancers.[1] Mutations may occur in the EGFR gene that results in increased activity. The presence of EGFR tyrosine kinase activating mutations has been found in 10–26% of NSCLC tumors. The presence of these mutations tends to increase the responsiveness of NSCLC patients to erlotinib, a tyrosine kinase inhibitor (TKI) that targets EGFR.[2] Erlotinib has demonstrated efficacy as a maintenance therapy and as second-line treatment of patients with advanced or metastatic NSCLC regardless of EGFR mutation status. However, the safety and efficacy profile of erlotinib compared to chemotherapy in white patients with EGFR mutations was unknown; previous studies have focused on Asian patients, who historically have different responses to NSCLC therapy than Western patients. Therefore, in 2006, the EURTAC [European Tarceva vs Chemotherapy] study was designed. In this prospective, randomized, phase III study, Gervais and associates compared erlotinib to platinum-based chemotherapy for the first-line treatment of Western patients with advanced NSCLC and EGFR activating mutations.[3]

Chemotherapy-naïve patients with advanced NSCLC (1,227 patients) were screened during a 5-year period, and 224 were identified as having EGFR-activating mutations. Of these patients, 174 were eligible for inclusion in the study. Inclusion criteria included stage IIIb or stage IV NSCLC, EGFR-activating mutations (deletions in exon 19 or mutation in exon 21 in the tyrosine kinase of the EGFR), chemotherapy-naïve (neoadjuvant or adjuvant therapy completed at least 6 months before enrollment), performance status of 2 or lower, and measurable or evaluable disease. Patients were randomized to receive erlotinib (150 mg/day) or 4 cycles of platinum-based chemotherapy (cisplatin [75 mg/m^2]/docetaxel [75 mg/m^2]; cisplatin [75 mg/m^2]/gemcitabine [1,250 mg/m^2, day 1 and 8]; docetaxel [75 mg/m^2]/carboplatin [area under the curve=6]; gemcitabine [1,000 mg/m^2, day 1 and 8]/carboplatin [area under the curve=5]). The primary endpoint was PFS, with the objective of demonstrating the superiority of erlotinib over platinum-based chemotherapy. Secondary endpoints included response, overall survival, and toxicity. In 2010, an independent data committee recommended that the study be closed because results from a planned interim analysis demonstrated that the primary objective had been met. The last patient was enrolled in January 2011.

The background and updated analysis of the study was presented. There were 87 patients in the chemotherapy arm and 86 patients in the erlotinib arm who were evaluable. The median age of patients in both arms was 65 years. In the chemotherapy arm, there were 19 men, 63 patients who had never smoked, 30 patients with a performance status of 0, 45 patients with a performance status of 1, and 78 patients with adenocarcinoma. In the erlotinib arm, there were 28 men, 57 patients who had never smoked, 27 patients with a performance status of 0, 47 patients with a performance status of 1, and 82 patients with adenocarcinoma.

The median PFS was significantly improved with erlotinib treatment. The median PFS in the chemotherapy arm was 5.2 months (95% CI, 4.5–6.0 months) versus 9.7 months (95% CI, 8.4–12.6 months) in the erlotinib arm (HR, 0.37; P<.0001). A subset analysis found that almost all patients benefited from treatment with erlotinib, with the exception of former smokers. However, there was an imbalance in baseline characteristics in this subset of patients. The ORR was also significantly improved for patients who received erlotinib compared to chemotherapy; the response rate was 14.9% in the chemotherapy arm and 58.1% in the erlotinib arm (P<.0001). The median survival was 22.9 months in the erlotinib arm and 18.8 months in the chemotherapy arm. At the time of the updated interim analysis, overall survival was ongoing, but there appeared to be no clear difference between the treatment arms. Dr. Gervais noted that while the analysis of toxicity was ongoing, there was a predictable rate of adverse events across all grades, including a higher rate of grade 3 and 4 adverse events in the chemotherapy arm.

At the interim analysis, the EURTAC study met its primary endpoint of PFS. This was the first study of white patients with NSCLC and EGFR-activating mutations conducted in the first-line setting. The investigators concluded that first-line treatment with erlotinib for patients with advanced NSCLC and EGFR mutations improved PFS compared to platinum-based chemotherapy, with a better tolerability profile. Screening advanced NSCLC patients for EGFR activating mutations may improve first-line therapy by identifying those patients who would most benefit from erlotinib treatment.

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Bevacizumab and Erlotinib in Treatment-Naïve Elderly Patients

In the United States, the median age of patients with newly diagnosed NSCLC is 71 years, and most patients with the disease are elderly (≥65 years). Systemic therapy is efficacious in older patients with a performance status of 0/1, the so-called "fit elderly." However, elderly patients are more likely to develop toxicities due to the presence of comorbid conditions and the progressive loss of organ function with age.[1] Until recently, there have been few clinical trials focusing on the treatment of older patients with advanced NSCLC. Therefore, successful treatment regimens that offer a lower risk of toxicity are needed to treat the fit elderly population with lung cancer. To that end, Borghaei and associates investigated the efficacy and tolerability of an all biologic-therapy regimen for the treatment of elderly patients with advanced NSCLC.[2] The study enrolled patients older than 65 years with treatment-naïve advanced NSCLC (stage IV or stage IIIB) between August 2007 and January 2011; EGFR status was not necessary for enrollment. The patients received erlotinib (150 mg/day) and bevacizumab (15 mg/kg every 3 weeks) in 21-day cycles. The primary endpoint of the study was PFS. Every 2 cycles, imaging was performed to document disease progression.

At the time of the report, data were available for 30 of the 33 patients accrued. Baseline patient characteristics included a median age of 74 years (range, 67–84 years), with 40% of the patients (n=12) older than 75 years. Half of the patients were female, 24 patients were white, 5 were African American, and 1 was Native American. There were 2 current smokers (6.7%), 23 former smokers (76.7%), and 5 never smokers (16.7%); the median pack-years exposure was 50 (range, 1–50; n=20 patients). Most patients had a comorbidity score of 0 (57%); the remaining patients had scores of 1 (32.1%), 2 (3.6%), and 3 (7.1%). Sixteen patients (62%) had an ECOG performance status of 1. At the time of enrollment, 7 patients (23.3%) had stage IIIB disease (AJCCv.6 criteria) and 23 patients (76.7%) had stage IV disease. Only 1 patient had received prior systemic treatment.

ABSTRACT SUMMARY The combination of erlotinib/bevacizumab in never-smokers with advanced lung adenocarcinoma: Southwest Oncology Group (SWOG) Trial 0636

One population of patients who may benefit from treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) is never-smokers with advanced lung adenocarcinoma. There is a higher prevalence of EGFR-activating mutations and/or copy number abnormalities in this subpopulation compared with other NSCLC patients. Patients with these mutations have improved clinical outcomes when treated with EGFR TKI therapies, such as erlotinib. In addition, combining bevacizumab with erlotinib may further increase clinical activity. Therefore, West and associates initiated a single-arm, phase II trial to determine if adding bevacizumab to erlotinib could improve clinical outcomes of never-smokers with advanced lung adenocarcinoma (Abstract MO09.03). The primary endpoint was overall survival. The study enrolled 89 patients who were never smokers (median age, 61.3 years). Most patients were treatment-naïve (87%), female (66%), white (66% white, 25% Asian) and had a performance status of 0/1 (97%). Patients received erlotinib (150 mg/day) and bevacizumab (15 mg/kg IV every 21 days) until disease progression or toxicity. The response rate was confirmed in 32% of patients and unconfirmed in an additional 13%. SD was observed in 38% of patients for a total nonprogression rate greater than 80%. The median PFS was 8 months; the analysis of overall survival is still ongoing. Of the 85 patients evaluable for toxicity, 14% discontinued due to adverse events. No unexpected adverse events occurred. There were no incidences of treatment-related deaths and 1 case of grade 3 pulmonary hemorrhage. A biomarker analysis found that 49% of patients (17 of 35) were EGFR FISH-positive, which correlated with improved PFS (HR, 0.35; 90% CI, 0.16–0.75; *P*=.01]. Patients with EGFR mutations (30%, 10 of 33) had a better Response Evaluation Criteria In Solid Tumors (RECIST) response rate (47% vs 26%; *P*=.03). The median PFS was 20 months for patients with FISH-positivity and/or EGFR mutations versus 6 months for patients with neither of these markers (*P*=.02). From these preliminary results, West and colleagues concluded that erlotinib plus bevacizumab resulted in promising efficacy and modest toxicity in never smokers with lung adenocarcinoma.

POSTER SUMMARY A phase II trial of pemetrexed (P), gemcitabine (G), and bevacizumab (BV) in untreated patients (pts) with advanced non-small cell lung cancer (NSCLC)

Wozniak and colleagues conducted a phase II trial that investigated a novel 2-week schedule of pemetrexed, gemcitabine, and bevacizumab for the treatment of advanced NSCLC (Poster P3.107). The study enrolled previously chemotherapy-naïve patients (performance scores of 0–1) with advanced nonsquamous NSCLC and sufficient hepatic, renal, and bone marrow function. Patients were treated with pemetrexed (500 mg/m^2), gemcitabine (1,500 mg/m^2), and bevacizumab (10 mg/kg) every 2 weeks for 12 cycles. However, the doses of pemetrexed and gemcitabine were reduced to 400 mg/m^2 and 1,200 mg/m^2, respectively, when the first 2 patients developed grade 4 neutropenia. Patients received bevacizumab until they experienced disease progression or toxicity. At the time of the report, 38 patients were evaluable for response (median age, 62 years; 56% were male; 87% had stage IV disease, 82% had adenocarcinoma). The median number of treatment cycles was 7 (range, 1–23 for pemetrexed/gemcitabine and 1–57 for bevacizumab). Response occurred in 16 patients (41%): 1 patient had a complete response, and 15 patients had partial responses. The median PFS was 6.1 months (95% CI, 3.9–7.6), and the 1-year PFS rate was 23% (95% CI, 10–36). The median overall survival was 18.7 months (95% CI, 8.1–27.4), and the 1-year overall survival rate was 61% (95% CI, 48–75). The median time to disease progression was 6.3 months (95% CI, 4–8.1). Twelve patients had stable disease (26%); the disease control rate was 67%. In the 39 patients evaluable for toxicity, the most common grade 3/4 toxicities included neutropenia (n=11), hyperglycemia (n=9), fatigue (n=7), elevated alanine transaminase/aspartate transaminase (n=4), dyspnea (n=4), leukopenia (n=3), and pain (n=3). One patient experienced a grade 5 hemoptysis off-treatment for progressive disease. The researchers concluded that pemetrexed, gemcitabine, and bevacizumab administered together had an acceptable toxicity profile with encouraging efficacy results.

The median time from the start of therapy to discontinuation was 4.8 months (95% CI, 1.7–14.9). The median number of treatment cycles for the patients who were off protocol was 4 (range, 1–40 cycles). The reasons for treatment discontinuation were progressive disease (13 patients), adverse events (4 patients), performance status of 2 (2 patients), physician decision (2 patients), patient withdrawal (1 patient), bowel perforation (1 patient), and bevacizumab-related proteinuria (1 patient). Six patients were still on protocol, with a range of 4 to 33 cycles. Seven patients (23.3%) required dose modifications.

The most common treatment-related grade 1 and grade 2 adverse events included diarrhea; constipation; epistaxis; dry, cracked skin; fatigue; vomiting; nausea; anorexia; rash; and weight loss. Treatment-related grade 3 adverse events were hypertension (7 patients), fatigue (1 patient), rash (3 patients), diarrhea (2 patients), anorexia (1 patient), infection with neutropenia (1 patient), bowel perforation (1 patient), and abnormal protein/creatine ratio (1 patient). One patient had treatment-related grade 4 diarrhea. A partial response was reported in 9 patients (30%), stable disease in 15 (50%), and progressive disease in 6 (20%). For all patients, the 1-year PFS was 27.6%, and the estimated median PFS was 6.6 months (95% CI, 3.6–14.9 months). The estimated 1-year overall survival was 60.7%, and the estimated median overall survival was 14.1 months (95% CI, 6.2 months–not reached); 14 of 26 patients have died. Data regarding smoking and EGFR status were collected, but the analysis is not yet complete.

The investigators concluded that first-line treatment with erlotinib and bevacizumab for patients older than 65 years with advanced NSCLC was effective and well-tolerated. The authors noted that no unexpected adverse events or toxicities were observed. A molecular analysis of the impact of smoking on treatment responses is ongoing.

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ECOG 4599: Clinical Characteristics and Outcomes of the Maintenance Bevacizumab Population

Vascular endothelial growth factor (VEGF) plays a central role in tumor angiogenesis. Continuous suppression of VEGF by bevacizumab has been demonstrated to control tumors in colorectal[1,2] and ovarian cancers.[3] In addition, preclinical studies have indicated that bevacizumab will be efficacious for the treatment of lung cancer, including NSCLC.[4,5] The ECOG 4599 study found that treatment-naïve patients with NSCLC had significantly improved median PFS (6.2 months vs 4.5 months; HR, 0.66; *P*<.0001) and overall survival (12.3 vs 10.3 months; HR, 0.79; *P*=.003) when bevacizumab was added to carboplatin and paclitaxel (CP).[6] However, limited data are available regarding the use of bevacizumab as a single-agent maintenance therapy in NSCLC. In this retrospective analysis, Sandler and colleagues assessed the clinical characteristics and outcomes of patients on maintenance bevacizumab in study ECOG 4599.[7]

Study ECOG 4599 enrolled 869 patients with advanced, metastatic, or recurrent nonsquamous NSCLC. For the induction phase, patients were randomized to receive CP alone (440 patients) or CP plus bevacizumab (15 mg/kg every 3 weeks; 429 patients) for 6 cycles. Patients in the CP plus bevacizumab arm who achieved an objective response or stable disease entered the maintenance phase with single-agent bevacizumab until progressive disease or excessive toxicity. This analysis was restricted to patients in the CP plus bevacizumab arm without progressive disease in the induction phase who received more than 1 infusion of maintenance bevacizumab (maintenance nonprogressors, 217 patients) and patients without progressive disease in the induction phase after 6 cycles of CP alone plus 21 days (CP nonprogressors, 134 patients). Response rates, PFS, overall survival, and 1-year survival rates were calculated using Kaplan-Meier methods. HRs were calculated using a Cox model that adjusted for baseline factors.

Overall, baseline patient characteristics were comparable between the bevacizumab maintenance group and the CP nonprogressors. In the induction phase, 60.1% of patients treated with CP plus bevacizumab (258 of 429 patients) and 44.1% of patients treated with CP alone (194 of 440 patients) completed all 6 cycles. In the CP plus bevacizumab arm, 48% of patients (n=207) received maintenance with

ABSTRACT SUMMARY Exploratory biomarker analyses from a placebo-controlled phase II study (OAM4558g) of MetMAb in combination with erlotinib in patients with advanced non-small-cell lung cancer (NSCLC)

Overactivation of the Met pathway has been implicated in numerous types of cancer, including NSCLC. MetMAb is a monovalent antibody to Met that prevents activation by hepatocyte growth factor. A phase II study of MetMAb in combination with erlotinib in previously treated patients with advanced NSCLC (n=128) found that overall survival was improved (HR, 0.37; *P*=.002) in Met-positive patients (n=65). Yu and associates analyzed archival tumor tissue samples from a study by Spigel and colleagues (Abstract 7505 from the 2011 American Society of Clinical Oncology Annual Meeting) to detect biomarkers related to Met and/or EGFR signaling (Abstract MO15.03). Fluorescence in situ hybridization (FISH), quantitative reverse transcriptase polymerase chain reaction, and various mutation detection techniques were used. In the 96 evaluable samples, the MET median copy number was 3.44 copies/cell (range, 1.6–25.0), with true gene amplification detected in 8% of samples. MET FISH positivity (≥5 copies/cell) was associated with a trend towards improved overall survival (HR, 0.47; *P*=.19). In patients with both MET and EGFR FISH copy number gains (n=23), there was an overall survival hazard ratio of 1.37 (95% CI, 0.43–4.36). Of the 112 evaluable samples, 13 EGFR mutations were detected (12%), and EGFR mutations were detected in 6 of the 7 patients with an objective response. KRAS mutations were detected in 23% of the samples (26 of 112), but the presence of this mutation did not appear to affect overall survival for patients receiving MetMab. Their analysis also found that high expression levels (at or exceeding the median) of MET, HGF, EGFR, AREG, or EREG mRNA were not independent predictors of improved overall survival. The authors concluded that the most sensitive independent predictor of overall survival benefit from MetMAb treatment was Met IHC.

ABSTRACT SUMMARY Phase 2 data for crizotinib (PF-02341066) in ALK-positive advanced non-small cell lung cancer (NSCLC): PROFILE 1005

Riely and associates presented preliminary results from an ongoing phase II trial of crizotinib for the treatment of patients with ALK-positive NSCLC (Abstract O31.05). This international trial enrolled patients with confirmed ALK-rearranged NSCLC with metastatic or recurrent disease after 1 or more chemotherapy regimens. Oral crizotinib (250 mg BID) was administered continuously in 3-week cycles. Every 3 weeks, safety and tolerability were evaluated. Every 6 weeks, disease response was assessed with the RECIST criteria. At the time of presentation, 136 patients were evaluable for safety, and 76 patients were evaluable for response (median age, 52 years; 94% with adenocarcinoma; 68% never-smokers; 53% female). Patients received a median of 9 weeks of crizotinib (range, 0.1–36 weeks). The ORR was 51%; 67 patients had PR and 1 patient had CR. SD was reported in 34% of patients, and the 12-week disease control rate was 74%. Progression occurred in 7 patients. Target lesion shrinkage occurred in 90% of patients. The most common treatment-related adverse events were primarily grade 1/2 and included nausea (46%), vision disorder (45%), vomiting (39%), and diarrhea (29%). Grade 3/4 adverse events occurred in 25% of patients. The most common treatment-related grade 3/4 events were increased alanine transaminase and neutropenia, which occurred in 7 patients; all other grade 3/4 adverse events were rare, occurring in 1 or 2 patients. Eight patients discontinued treatment, including 3 patients with poor liver function tests and 2 patients with pneumonitis. Two treatment-related deaths occurred. The preliminary data from this study suggest that crizotinib was safe and well-tolerated in patients with previously treated ALK-rearranged NSCLC. In addition, these data indicate that crizotinib has clinically meaningful antitumor activity in these patients.

bevacizumab without prior progressive disease; patients received a median of 12 cycles of bevacizumab (induction plus maintenance). One year after the start of the induction phase, 75% of the patients in the bevacizumab maintenance group (162 of 217 patients) and 69% of the CP nonprogressor group (92 of 134 patients) were alive and still enrolled in the study.

Among those patients who received bevacizumab during maintenance (n=234), 1.9% had CR, 55.6% had PR, 30.4% had stable disease, and 12.1% had an unknown response. In the CP nonprogressor group (n=134), 2.3% had CR, 31.3% had PR, 42.0% had stable disease, and 24.4% were unknown. The median postinduction PFS (starting from day 1 of cycle 7) was significantly longer in the bevacizumab maintenance group compared to the CP nonprogressor group (4.4 months vs 2.8 months, respectively; HR, 0.64; $P<.001$). The median PFS from the start of treatment was 8.7 months and 7.2 months, respectively. The median postinduction overall survival was also significantly longer in the bevacizumab maintenance group compared to the CP nonprogressor group (12.8 vs 11.4 months, respectively; HR, 0.75; $P=.030$). The median overall survival from the start of treatment was 17.0 months in the bevacizumab maintenance group and 15.8 months in the CP nonprogressor group. The 1-year survival rate was improved in the bevacizumab maintenance group compared to the CP nonprogressor group (74.9% vs 67.9%, respectively). Patients receiving bevacizumab maintenance had higher rates of 2-year overall survival (34% bevacizumab maintenance vs 25% CP nonprogressor) and 1-year PFS (32% bevacizumab maintenance vs 17% CP nonprogressor).

There appeared to be no significant differences in toxicity between maintenance bevacizumab and CP plus bevacizumab. The primary reasons for discontinuation of bevacizumab were progressive disease (70%) and toxicity (10%). Treatment-related grade 3, 4, or 5 adverse events occurred more frequently during the induction phase than the maintenance phase. During postinduction therapy with bevacizumab, there were 13.8% grade 3 events, the most common of which was fatigue (3.2% of patients). Other grade 3 adverse events included febrile neutropenia, infection with neutropenia, sensory neuropathy, motor neuropathy, hypertension, thrombosis/embolism, dyspnea, proteinuria, and hemorrhage. Grade 4 adverse events occurred in 5.5% of patients; the most common was thrombosis/embolism (0.9%). Other grade 4 events were arrhythmia, hypertension, proteinuria, and hemorrhage. Only 1.8% of patients experienced grade 5 events, which included arrhythmia (0.5%), cardiac ischemia (0.5%), and hemorrhage (0.9%).

The investigators concluded that patients with advanced, metastatic, or recurrent nonsquamous NSCLC who received CP plus bevacizumab induction followed by bevacizumab maintenance in this study had significant reductions in HRs for progression and survival compared to CP induction therapy alone. This study suggests there is a benefit to bevacizumab maintenance therapy; however, the authors noted that the study was retrospective and noncomparative.

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ABSTRACT SUMMARY British Thoracic Oncology Group Trial, BTOG2: randomised phase III clinical trial of gemcitabine combined with cisplatin 50 mg/m^2 (GC50) versus cisplatin 80 mg/m^2 (GC80) versus carboplatin AUC 6 (GCb6) in advanced NSCLC

In this phase III trial from the British Thoracic Oncology Group, 1,363 patients were randomized to receive gemcitabine (1,250 mg/m^2) combined with cisplatin at 1 of 3 doses: 50 mg/m^2, 80 mg/m^2, or area under the curve (AUC) of 6, for up to 4 cycles (Abstract O01.03). Eligibility criteria included histologically proven NSCLC, performance status of 0–2, stage IIIB/IV disease, and a glomerular filtration rate of greater than 60 mL per minute. The median age of the patients was 63 years. Performance status was 0 in 32%, 1 in 60%, and 2 in 8%. Patients were randomized between April 2005 and November 2009. At the time of the analysis, 140 patients were alive. The median follow-up was 21 months. The response rates were 23% in the 50 mg/m^2 arm, 33% in the 80 mg/m^2 arm, and 28% in the AUC 6 arm (P=.01). Median survival rates were 8.3 months in the 50 mg/m^2 arm, 9.5 months in the 80 mg/m^2 arm, and 10.0 months in the AUC 6 arm. (Statistical significance was achieved when comparing the 50 mg/m^2 arm with the other 2.) At least 1 adverse event of grade 3 or 4 occurred in 27% of patients in the 50 mg/m^2 arm, 41% of patients in the 80 mg/m^2 arm, and 57% of patients in the AUC 6 arm.

Crizotinib in ALK-Positive Patients

Activating mutations and translocations of the anaplastic lymphoma kinase gene (ALK) are associated with various types of carcinomas. Crizotinib is a small-molecule, competitive, selective inhibitor of ALK and MET tyrosine kinases. This agent targets an ALK fusion gene rearrangement, EML4-ALK, which is found in approximately 4–5% of patients with NSCLC.[1] This mutation is most prevalent in never smokers/light smokers and in patients with adenocarcinoma. A previous phase I trial of 82 patients with ALK-positive NSCLC found that treatment with crizotinib (250 mg twice daily in 28-day cycles) resulted in an ORR of 61%, a median PFS of 10 months, and stable disease in 33% of patients.[2] The impact of crizotinib on overall survival data has not yet been assessed. Therefore, Shaw and colleagues investigated the overall survival of ALK-positive patients treated with crizotinib in the phase I trial, assessed the impact of crizotinib treatment on overall survival in ALK-positive NSCLC patients compared to historical matched-control patients, and compared the survival outcomes of crizotinib-naïve ALK-positive patients versus ALK-negative patients.[3]

Although overall survival is typically determined in a randomized controlled study, the identification of overall survival benefits can be challenging due to confounding by poststudy treatments. In the absence of randomized data, the approach used by Dr. Shaw and associates to determine survival benefit was to compare the overall survival of crizotinib-treated patients with that of a comparative population of crizotinib-naïve patients. The overall survival of 82 ALK-positive NSCLC patients treated with crizotinib was determined using data from an international phase I clinical trial.[2] This study enrolled patients from the United States, Australia, and Korea. For ALK-positive controls, data were collected from 37 ALK-positive patients with advanced NSCLC from the United States and Australia who were not treated with crizotinib. The

ABSTRACT SUMMARY Aflibercept in combination with docetaxel for second-line treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC): final results of a multinational placebo-controlled phase III trial (EFC10261-VITAL)

Aflibercept is a recombinant fusion protein that acts as a decoy receptor, preventing all forms of VEGF-A and placental growth factor from interacting with their receptors. Evidence suggests that aflibercept, in combination with docetaxel, may be beneficial for the treatment of recurrent NSCLC. Novello and colleagues presented the final results of the VITAL (A Multinational, Randomized, Double-Blind Study Comparing Aflibercept Versus Placebo in Patients Treated with Second-Line Docetaxel after Failure of One Platinum Based Therapy for Locally Advanced or Metastatic Non-Small-Cell Lung Cancer) study, a phase III trial investigating the use of aflibercept plus docetaxel for the treatment of patients with stage III or stage IV non-squamous NSCLC (performance status 0–2) who had failed 1 prior platinum-based therapy (Abstract O43.06). The primary endpoint was overall survival. The trial enrolled 913 patients (median age, 60 years; 66% male; 89% white; 83% with adenocarcinoma; 90% with metastatic disease, 12.3% with prior bevacizumab) who were randomized 1:1 to receive docetaxel (75 mg/m^2) plus either aflibercept (6 mg/kg) or placebo every 3 weeks. As of January 11, 2011, the median follow-up was 23.0 months. At that time, 95% of patients had progressed, and 75.2% had died. The median overall survival was 10.05 months in the docetaxel plus aflibercept arm and 10.41 months in the docetaxel plus placebo arm (HR, 1.01; 95% CI, 0.87–1.17; *P*=.898). The addition of aflibercept improved PFS (docetaxel plus aflibercept, 5.19 months vs docetaxel plus placebo, 4.11 months; HR, 0.82; 95% CI, 0.72–0.94; *P*=.0035) and ORR (23.3% vs 8.9%; *P*<.0001). Treatment with aflibercept was associated with a higher incidence of stomatitis, weight decrease, hypertension, epistaxis, and dysphonia. Treatment discontinuation due to adverse events occurred in 27.2% of the patients who received docetaxel plus aflibercept and 14.6% of the patients who received docetaxel plus placebo. The most common reasons for discontinuation in the aflibercept arm included infections (5.5%), proteinuria (2.7%), asthenia/fatigue (2.4%), and death (2.2%). The authors noted that the study did not meet its primary endpoint of overall survival, but the addition of aflibercept to docetaxel improved PFS and ORR in patients with advanced recurrent NSCLC.

ALK-negative controls included 253 advanced NSCLC outpatients at Massachusetts General Hospital who were ALK-negative, EGFR wild type, and crizotinib-naïve.

The median overall survival of the 82 ALK-positive patients treated with crizotinib had not yet been reached. The 1-year overall survival of this group was 74%, and the 2-year overall survival was 54%. Sex (*P*=.35), ethnicity (Asian vs non-Asian; *P*=.46), smoking history (never vs any smoking; *P*=.82), or age (60 years or younger vs older than 60; *P*=.93) did not result in significant differences in overall survival. The median overall survival from the date of metastatic diagnosis of the ALK-positive controls was 20 months, with a 1-year overall survival of 73% and a 2-year overall survival of 33%.

In the original study, the crizotinib-treatment group included patients enrolled in Korea, and the ALK-positive control patients were enrolled outside Korea. Therefore, Shaw and colleagues compared the non-Korean cohort of crizotinib-treated patients (n=56 patients) to the ALK-positive control group (n=36 patients). The groups did not differ significantly in either demographic or clinical pathologic characteristics, including age, sex, smoking status, presence of brain metastases, mean number of prior therapies, or types of prior chemotherapy. The ALK-positive patients were significantly younger than the ALK-negative controls and were more likely to be never or light smokers, which is consistent with the published literature.

The crizotinib-treated ALK-positive patients had variable numbers of prior therapies, and almost one-third of these patients had received 3 or more prior treatments for metastatic disease. To minimize skewing of the survival results, the investigators examined the survival outcomes of less heavily pretreated patients. The overall survival of the 32 ALK-positive patients who were treated with second-line or third-line crizotinib was longer than the overall survival of the 23 ALK-positive controls who were treated with any second-line therapy (not reached vs 6 months, respectively; *P*=.004). For these subsets of patients, the 1-year overall survival was 71% and 46%, respectively, and the 2-year overall survival was 61% and 9%, respectively. The overall survival of ALK-positive patients treated with second-line or third-line crizotinib was also longer than the overall survival of the 123 ALK-negative control patients who received any second-line therapy; the median overall survival of the ALK-negative control patients was 11 months from the time of second-line therapy, the 1-year overall survival was 49%, and the 2-year overall survival

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Avastin PI

Avastin PI

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was 33%. These results suggest that crizotinib may significantly improve survival outcomes in patients with advanced ALK-positive NSCLC.

Because pathologic features associated with the presence of the ALK-positive fusion gene may influence prognosis, survival was analyzed in subsets of control patients. For example, in the subset of patients with adenocarcinoma histology who were never or light smokers, the overall survival from time of metastatic disease was comparable between the 29 ALK-positive controls and 84 ALK-negative wild-type controls (median overall survival, approximately 19–20 months for both groups; HR, 0.93; *P*=.79). These results suggest that in the absence of crizotinib therapy, ALK-positive patients have similar survival outcomes to ALK-negative wild-type control patients.

This study had several limitations: it was retrospective, nonrandomized, and the number of patients was small. Despite the limitations, Dr. Shaw noted that the results are significant. The investigators concluded that treatment with second-line or third-line crizotinib is associated with longer overall survival in ALK-positive patients with NSCLC relative to comparable crizotinib-naïve patients.

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ABSTRACT SUMMARY Outcome of advanced NSCLC patients with EGFR exon 19 and 21 mutations treated with erlotinib (E) alone or in combination with carboplatin/paclitaxel (CP) in CALGB 30406

In the phase II Cancer and Leukemia Group B study 30406, Janne and associates prospectively assessed whether EGFR mutations affected the outcome of chemotherapy-naïve patients with advanced lung adenocarcinoma (never or light former smokers) who were treated with erlotinib alone or in combination with carboplatin/paclitaxel (Abstract O39.01). Patients were randomized to receive erlotinib alone (150 mg/day; 81 patients) or combined with carboplatin/paclitaxel (erlotinib, 150 mg/day administered continuously; carboplatin, at an area under the curve of 6 every 21 days; and paclitaxel, 200 mg/m^2 every 21 days; 100 patients) for 6 cycles followed by erlotinib. The baseline characteristics were similar between the treatment arms. After a median follow-up of 38 months, 67% of the patients had died. Grade 3/4 hematologic toxicity occurred in 2% of the erlotinib arm and 49% of the erlotinib plus carboplatin/paclitaxel arm; grade 3/4 nonhematologic toxicity occurred in 24% of the erlotinib arm and 52% of the erlotinib plus carboplatin/paclitaxel arm. Relative risk (erlotinib arm: EGFR mutant, 70% vs wild type, 9%; erlotinib plus carboplatin/paclitaxel arm: 73% vs 30%; *P*<.0001, both arms), PFS (erlotinib arm: 14.1 months vs 2.6 months; erlotinib plus carboplatin/paclitaxel arm: 17.2 months vs 4.8 months; *P*<.0001, both arms), and overall survival (erlotinib arm: 31.3 months vs 18.1 months; *P*=.0198; erlotinib plus carboplatin/paclitaxel arm: 38.1 months vs 14.4 months; *P*=.011) were significantly better in patients with EGFR mutations. The overall survival for patients with EGFR mutations was slightly, but not significantly, longer with erlotinib plus carboplatin/paclitaxel versus erlotinib treatment (38 months vs 31 months; *P*=.9227). Patients with the exon 19 deletion had improved relative risk (79% vs 59%; *P*=.0743) and PFS (17.7 months vs 12.1 months; *P*=.1777) compared to patients with the L858R mutation. There was also a trend toward improved PFS in patients with the exon 19 deletion treated with erlotinib plus carboplatin/paclitaxel compared to erlotinib (27.5 months vs 15.7 months; *P*=.2153). The authors concluded that both erlotinib and erlotinib plus carboplatin/paclitaxel are effective first-line treatment options for patients with EGFR-mutant NSCLC; however, patients with the exon 19 deletion may have improved outcomes relative to patients with L858R mutations.

ECOG E1505: Adjuvant Chemotherapy With or Without Bevacizumab for Completely Resected, Early Stage NSCLC

Adjuvant chemotherapy after resection has been shown to increase absolute survival in patients with early stage NSCLC. In addition, a 2006 Eastern Cooperative Oncology Group (ECOG) study by Sandler and associates showed that when bevacizumab was added to a treatment regimen of carboplatin and paclitaxel, previously untreated patients with advanced NSCLC had significantly improved PFS and overall survival compared with patients who received carboplatin and paclitaxel alone.[1] The results of this study suggested that bevacizumab might be successfully used with adjuvant chemotherapy. As such, Wakelee and associates initiated a randomized, phase III study (ECOG 1505) to determine if the addition of bevacizumab to chemotherapy could improve the survival of patients with completely resected, early-stage NSCLC.[2]

Target enrollment for study ECOG 1505 is 1,500 patients. Inclusion criteria include resected stage IB (at least 4 cm in size) through IIIA NSCLC (according to the sixth edition of the staging system from the American Joint Committee on Cancer); resection within 6–12 weeks of enrollment; limited lymph node sampling (level 7 for all patients, level 4R for right-sided tumors, level 5 or 6 for left-sided tumors); ECOG performance status of 0–1; no prior chemotherapy except for low-dose methotrexate for nonmalignant conditions administered more than 2 weeks prior to randomization; no radiation, hormonal, or other therapy for cancer within 5 years of randomization; and no planned post-operation radiation therapy.

Exclusion criteria included recent major surgery, uncontrolled hypertension, serious nonhealing wounds, or history of cerebral vascular accident or transient ischemic attack. Patients were stratified according to type of chemotherapy, disease stage, histology, and sex. Patients were random-

ABSTRACT SUMMARY Epidermal growth factor receptor (EGFR) expression as a predictor of survival for first-line chemotherapy plus cetuximab in FLEX study patients with advanced non-small cell lung cancer (NSCLC)

To define a predictive biomarker of response to chemotherapy plus cetuximab, Pirker and coworkers analyzed patients from the FLEX (Cetuximab Plus Chemotherapy in Patients with Advanced Non-Small-Cell Lung Cancer) study to evaluate if there was an association between tumor epidermal growth factor receptor (EGFR) expression levels and clinical outcome (Abstract 1538). To determine tumor EGFR expression levels, immunohistochemistry (IHC) of samples from 1,121 FLEX study patients was performed. Patients were grouped according to low tumor EGFR expression (<200) or high tumor EGFR expression (≥200). In those patients with high EGFR expression (345 patients; 31%), the addition of cetuximab to chemotherapy significantly prolonged overall survival (12.0 months vs 9.6 months, respectively; HR, 0.73; *P*=.011) and improved the objective response rate (ORR; 44.4 vs 28.1, respectively; odds ratio, 2.04; *P*=.002) compared to chemotherapy alone. However, this treatment benefit was not observed for those patients with low EGFR expression (776 patients; 69%). A treatment interaction test revealed that the difference in hazard ratios for overall survival between the EGFR expression groups was significant (*P*=.044). In patients with high EGFR expression, there were significant improvements in relative risk and time-to-treatment failure, and a nonsignificant improvement in PFS with the addition of cetuximab to chemotherapy. There were no differences in relative risk, time-to-treatment failure, or PFS in the low EGFR expression group. There was no observable difference in the safety profiles between the 2 EGFR expression profiles. Pirker and colleagues concluded that chemotherapy plus cetuximab improved overall survival in advanced NSCLC patients with high tumor EGFR expression. They suggested that EGFR expression levels may serve as a biomarker for identifying those patients who would most benefit from receiving first-line therapy with chemotherapy plus cetuximab.

ized 1:1 to receive doublet chemotherapy (cisplatin [75 mg/m^2 on day 1] plus vinorelbine [30 mg/m^2, days 1 and 8], docetaxel [75 mg/m^2 on day 1], gemcitabine [1,200 mg/m^2 on days 1 and 8], or pemetrexed [500 mg/m^2 on day 1; nonsquamous NSCLC only]) alone or in combination with bevacizumab (15 mg/kg on day 1). Patients received treatment every 3 weeks for 4 cycles or until they experienced disease progression or unacceptable toxicity.

Bevacizumab was continued for up to 1 year after completion of 4 cycles of chemotherapy or until disease recurrence or unacceptable toxicity. The primary endpoint of the study was overall survival. The secondary endpoints were disease-free survival, toxicity, identification of predictive factors of clinical outcome, and the potential correlation between smoking and clinical outcome. Patients in the study will be periodically followed-up for 10 years.

Dr. Wakelee presented interim patient demographic data and toxicity results. The interim toxicity analysis included data from patients who had been randomized at least 1 year before the data pull date. To test for the association between the treatment arm and categorical variables, Fisher's exact test was used. To test for an association between treatment differences in continuous variables, the Wilcoxon rank sum test was used.

There were 591 patients included in the interim analysis (299 patients in the chemotherapy arm and 292 patients in the chemotherapy plus bevacizumab arm), with demographics well balanced among the arms. The median age of the patients was 61 years (range, 35–86 years), and 360 patients (61%) had an ECOG performance status of 0. There were slightly more women (52%) than men; 88% of patients were white, 54% had adenocarcinoma, and 31% had squamous histology. The disease stage of the enrolled patients was 23% IB (137 patients), 44% II (259 patients), 28% IIIA-N2 (167 patients), and 4% IIIA-T3N1 (23 patients). Pneumonectomy had been performed in 13% (75 patients). There were 160 patients (27%) who received cisplatin/vinorelbine, 196 patients (33%) who received cisplatin/docetaxel, 155 patients (26%) who received cisplatin/gemcitabine, and 82 patients (14%) who received cisplatin/pemetrexed (administered only to patients with nonsquamous NSCLC).

With the addition of bevacizumab, there was an overall increase in grade 3/4 toxicity (68.0% chemotherapy alone vs 84.0% chemotherapy plus bevacizumab; P<.001). In particular, there was a significant increase in the risk of grade 3/4 hypertension (2.0% vs 19.6%; P<.001), proteinuria (0.7% vs 3.2%; P=.03), and abdominal pain (0.3% vs 4.6%; P=.001). Dr. Wakelee noted that the cause of the abdominal pain was currently under investigation, although it was not due to perforation. There was also a slight increase in neutropenia and lymphopenia with bevacizumab therapy.

POSTER SUMMARY Docetaxel (D) and cisplatin (C) induction chemotherapy followed by biweekly D and C with concurrent thoracic radiotherapy for stage III non-small cell lung cancer (NSCLC). A Galician Lung Cancer Group study.

This study from the Galician Lung Cancer Group evaluated the feasibility of induction chemotherapy with docetaxel and cisplatin followed by concurrent chemoradiation with biweekly docetaxel and cisplatin (Poster P4.241). The patients had inoperable, locally advanced NSCLC, at stage IIIAN2/IIIB (no pleural T4). Their mean age was 61 years. The patients were included in a phase II study with induction chemotherapy consisting of 3 cycles of docetaxel 75 mg/m^2 on day 1 and cisplatin 40 mg/m^2 days 1–2 every 3 weeks. Patients who did not require surgery and whose disease did not progress underwent concurrent chemoradiation with docetaxel 30 mg/m^2 and cisplatin 30 mg/m^2 every 2 weeks for 4 courses, during conformal thoracic radiotherapy (60-66 Gys, 180 cGy/day). The median follow-up was 16 months. During the induction docetaxel and cisplatin phase, among the 78 patients evaluable for response, there were 2 complete responses, 46 partial responses, and 9 cases of progressive disease. Median progression-free survival was 11 months, and median overall survival was 19 months. Nine patients underwent surgery. Among the 55 patients who completed the concurrent chemoradiation phase and were evaluable for response, there were 8 complete responses, 37 partial responses, 3 cases of stable disease, and 7 cases of progressive disease. Progression-free survival was 46% at 1 year and 21% at 2 years. Overall survival was 64% at 1 year and 33% at 2 years. During the docetaxel and cisplatin phase, the most common grade 3/4 adverse events among the 82 evaluable patients were neutropenia, diarrhea, nausea/vomiting, and anemia. There were 10 episodes of febrile neutropenia and 1 treatment-related death. Among the patients who received concurrent chemoradiation, the most common toxicities were grade 1/2 grade esophagitis, grade 1/2 anemia, and grade 1/2 pneumonitis. There was 1 treatment-related death.

There were no significant differences in the rates of grade 3/4 anemia, fatigue, dehydration, central nervous system ischemia, or hemorrhage. Although grade 5 toxicity was observed, the rates did not differ significantly between the chemotherapy alone arm and the chemotherapy plus bevacizumab arm (2.4% vs 3.6%; *P*=.46). There were 8 on-treatment deaths in the chemotherapy alone arm and 10 on-treatment deaths in the chemotherapy plus bevacizumab arm. In the chemotherapy alone arm, the deaths were primarily due to disease progression; in the chemotherapy plus bevacizumab arm, deaths were caused by cardiac ischemia, hypoxia, febrile neutropenia, lung hemorrhage, and disease progression. There was 1 sudden death and 1 case of nonfatal bronchopleural fistula among patients in the chemotherapy plus bevacizumab arm.

The results of this interim analysis indicate that there are no unexpected toxicities associated with the addition of bevacizumab to 4 different cisplatin-containing chemotherapy regimens. Dr. Wakelee noted that there have been challenges with enrollment due to lack of lymph node sampling in patients who would have otherwise been eligible for study inclusion, as well as reluctance on the part of patients to enter into 1 year of treatment. The ECOG 1505 study is ongoing, with accrual of approximately 20 patients per month and a projected completion of enrollment in 2013.

POSTER SUMMARY Erlotinib in advanced non-small cell lung cancer (NSCLC) treatment

Gonçalves and colleagues performed an observational study analysis in patients with advanced NSCLC who received erlotinib as second-line and third-line therapy between 2006 and 2010 to assess for response according to molecular status (Poster P3.197). Among the 104 patients included in the study, 43 were in stage III, 52 were in stage IV, and 9 were in early stages. There were 57 men and 47 women, with a mean age of 67.2 years; 48 were non-smokers, 31 were ex-smokers, and 25 were smokers. Types of NSCLC included adenocarcinoma in 66 patients, squamous cell in 18 patients, and undifferentiated carcinoma in 20 patients. The first-line chemotherapy regimens included platinum plus gemcitabine (51.0%), platinum plus vinorelbine (11.5%), platinum plus paclitaxel (11.5%), and platinum plus pemetrexed (8.6%). When erlotinib was used as third-line therapy, the most common second-line regimens were pemetrexed (61.1%) and docetaxel (30.6%). EGFR mutation testing was performed in 82 patients; it was positive in 22. Overall survival was assessed in all patients, except for those in early stage and IIIA disease. The EGFR-positive patients had an overall survival of 47 months as compared with 22 months in the EGFR-negative patients (*P*=.038). Among all patients, partial remission occurred in 12.1%, stable disease was shown in 40.7%, and progressive disease occurred in 47.2%. Among the EGFR-positive patients, 15.0% had a partial response, stable disease occurred in 50.0%, and progressive disease occurred in 35.0%. In patients who were EGFR-positive, the response to erlotinib was associated with better control of the disease as compared with patients who were EGFR-negative. The estimated survival after treatment with erlotinib was 14 months in EGFR-positive patients and 6 months in EGFR-negative patients (*P*=.003).

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Commentary

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The International Association for the Study of Lung Cancer (IASLC) 16th World Conference on Lung Cancer, held on July 3–7 in Amsterdam, featured many studies in non–small cell lung cancer (NSCLC) with important implications for patient care. New data were presented regarding single-agent therapy, combination regimens, and novel agents.

The PARAMOUNT (Phase III Study of Maintenance Pemetrexed [Pem] Plus Best Supportive Care [BSC] Versus Placebo Plus BSC Immediately Following Induction Treatment With Pem Plus Cisplatin for Advanced Nonsquamous Non-Small Cell Lung Cancer) trial by Paz-Ares and colleagues is another example of how maintenance therapy is coming to the mainstream of treatment for advanced lung cancer.[1] The risk of disease progression was reduced by 36% among patients who received pemetrexed continuation maintenance therapy. The PARAMOUNT trial demonstrated that maintenance therapy with pemetrexed improved progression-free survival in patients who received pemetrexed as frontline therapy, an outcome suggesting that this approach might be a standard treatment strategy for patients with advanced disease. We are still waiting for the results of overall survival from this study, which are expected sometime soon.

The FLEX (Cetuximab Plus Chemotherapy in Patients With Advanced Non-Small-Cell Lung Cancer) study was presented at the Annual Meeting of the American Society of Clinical Oncology (ASCO) 2 years ago.[2] This study examined the effect of cetuximab added to cisplatin and vinorelbine as compared with cetux-

ABSTRACT SUMMARY Epidermal growth factor receptor (EGFR) expression as a predictor of survival for first-line chemotherapy plus cetuximab in FLEX study patients with advanced non-small cell lung cancer (NSCLC)

To define a predictive biomarker of response to chemotherapy plus cetuximab, Pirker and coworkers analyzed patients from the FLEX (Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer) study to evaluate if there was an association between tumor epidermal growth factor receptor (EGFR) expression levels and clinical outcome (Abstract 1538). To determine tumor EGFR expression levels, immunohistochemistry (IHC) of samples from 1,121 FLEX study patients was performed. Patients were grouped according to low tumor EGFR expression (<200) or high tumor EGFR expression (≥200). In those patients with high EGFR expression (345 patients; 31%), the addition of cetuximab to chemotherapy significantly prolonged overall survival (12.0 months vs 9.6 months, respectively; HR, 0.73; *P*=.011) and improved the objective response rate (ORR; 44.4 vs 28.1, respectively; odds ratio, 2.04; *P*=.002) compared to chemotherapy alone. However, this treatment benefit was not observed for those patients with low EGFR expression (776 patients; 69%). A treatment interaction test revealed that the difference in hazard ratios for overall survival between the EGFR expression groups was significant (*P*=.044). In patients with high EGFR expression, there were significant improvements in RR and time-to-treatment failure, and a nonsignificant improvement in PFS with the addition of cetuximab to chemotherapy. There were no differences in RR, time-to-treatment failure or PFS in the low EGFR expression group. There was no observable difference in the safety profiles between the 2 EGFR expression profiles. Pirker and colleagues concluded that chemotherapy plus cetuximab improved overall survival in advanced NSCLC patients with high tumor EGFR expression. EGFR expression levels may serve as a biomarker for identifying those patients who would most benefit from first-line therapy with chemotherapy plus cetuximab.

imab and vinorelbine alone in patients with advanced NSCLC. There was a small improvement in overall survival among patients in the cetuximab arm (median, 11.3 months vs 10.1 months [*P*=.0441]). Pirker and colleagues presented results from an immunochemistry analysis that utilized the H score, which identified the top 33% of patients with the most highly determined immunostaining for epidermal growth factor receptor (EGFR) in the tumor tissue.[3] In this group of patients, the hazard ratio improved significantly, demonstrating an increased overall survival. This finding suggests that the H score, if validated, could be used to identify patients who would benefit the most from therapy with EGFR inhibitors. The Southwest Oncology Group (SWOG) is conducting a large, randomized study with cetuximab (SWOG 0819), which will now incorporate the H score into the analysis.

The EURTAC (European Erlotinib Versus Chemotherapy) trial by Gervais and associates compared the EGFR inhibitor erlotinib versus chemotherapy in a Western population of patients with EGFR gene mutations.[4] In patients receiving erlotinib, progression-free survival was 9.7 months, a significant improvement over patients receiving chemotherapy, who achieved progression-free survival of 5.2 months. This study again shows that progression-free survival is greatly improved for patients who receive erlotinib versus chemotherapy in this setting. It suggests that the use of EGFR inhibitors as frontline therapy is likely to become the standard of care. This study did not show a survival benefit, as it remains immature. However, it will be difficult to show a survival benefit in this study, given the patient crossover.

Thongprasert and colleagues examined a subset of East Asian patients participating in a phase III trial of sunitinib plus erlotinib for the treatment of advanced NSCLC.[5] Among patients who received erlotinib plus sunitinib, the overall response rate was 38.5%, as compared with 13.7% among patients in the control group (*P*=.0083). The addition of sunitinib to erlotinib increased the median overall survival and resulted in 1 confirmed complete response. It has long been known that there is a preclinical and early clinical trial advantage to combining an EGFR inhibitor and an angiogenesis inhibitor. This approach enables one to target both the tumor and the microenvironment.

Trial 0636 from the SWOG, which examined the combination of erlotinib/bevacizumab in never-smokers with advanced lung adenocarcinoma, again shows that the idea of an angiogenesis inhibitor and an EGFR inhibitor is certainly one of great interest.[6] This combination in a never-smoking population showed some signs of early activity and safety. The erlotinib/bevacizumab combination achieved a response in 32% of patients (response was unconfirmed in an additional 13%). The total nonprogression rate was greater than 80%.

In a large study by Novello and associates, docetaxel in combination with the anti-VEGF agent aflibercept was examined in the second-line setting. Progression-free survival and overall response rate were significantly improved with the addition of aflibercept. However, overall survival was not improved. This outcome suggests that we are going to need to further explore for biomarkers to identify the combination that will be most beneficial.

Summary

All these trials really show how targeted therapies are having an impact on patient outcome in advanced NSCLC. Now it will be critical to combine molecular profiling with clinical care and clinical studies to truly find the right drug (or drug combinations) for a given patient.

Acknowledgment

Dr. Herbst has no real or apparent conflicts of interest to report.

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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).]*

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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.

AVASTIN® (bevacizumab)

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.

Genentech
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Avastin® (bevacizumab)

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94080-4990

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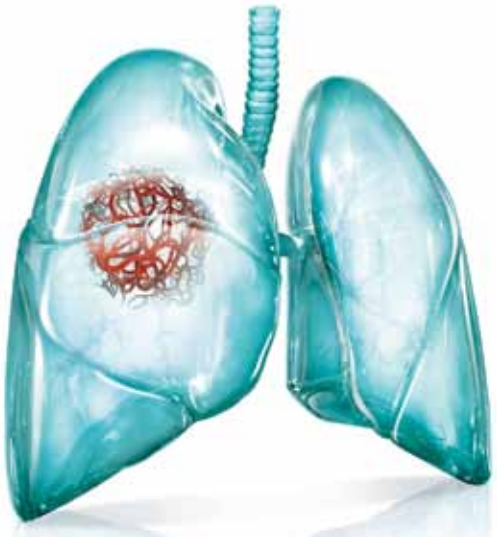
Initial U.S.Approval: February 2004
Code Revision Date: February 2011

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

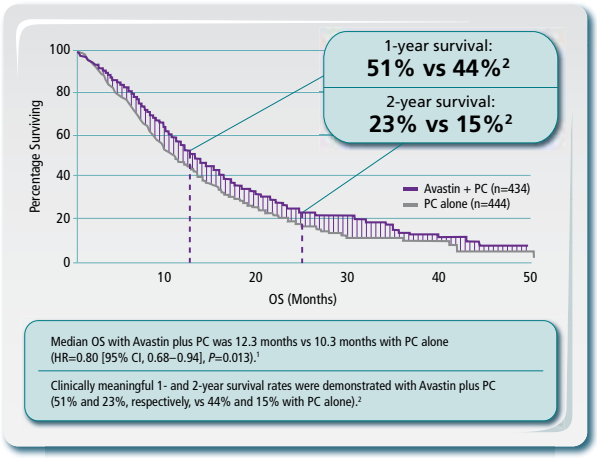
Think Avastin

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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