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A SPECIAL MEETING REVIEW EDITION

Highlights in NSCLC From the 2012 American Society of Clinical Oncology Annual Meeting

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- AvaALL: Open-Label Randomized Phase IIIb Trial Evaluating the Efficacy and Safety of Standard of Care With or Without Continuous Bevacizumab (BV) Treatment Beyond Disease Progression in Patients (pts) With Advanced Nonsquamous Non-Small Cell Lung Cancer (NSCLC) After First-Line (1L) Treatment With BV Plus Platinum-Doublet Chemotherapy (CT)
- LUX-Lung 3: A Randomized, Open-Label, Phase III Study of Afatinib Versus Pemetrexed and Cisplatin as First-Line Treatment for Patients With Advanced Adenocarcinoma of the Lung Harboring EGFR-Activating Mutations
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- PARAMOUNT: Final Overall Survival (OS) Results of the Phase III Study of Maintenance Pemetrexed (pem) Plus Best Supportive Care (BSC) Versus Placebo (plb) Plus BSC Immediately Following Induction Treatment With Pem Plus Cisplatin (Cis) for Advanced Nonsquamous (NS) Non-Small Cell Lung Cancer (NSCLC)
- Phase II Double-Blind, Randomized Study of Selumetinib (SEL) Plus Docetaxel (DOC) Versus DOC Plus Placebo as Second-Line Treatment for Advanced KRAS Mutant Non-Small Cell Lung Cancer (NSCLC)
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PLUS Meeting Abstract Summaries

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AvaALL: Open-Label Randomized Phase IIIb Trial Evaluating the Efficacy and Safety of Standard of Care With or Without Continuous Bevacizumab (BV) Treatment Beyond Disease Progression in Patients (pts) With Advanced Nonsquamous Non-Small Cell Lung Cancer (NSCLC) After First-Line (1L) Treatment With BV Plus Platinum-Doublet Chemotherapy (CT)

Prognosis and survival rates are very poor for patients with advanced non–small cell lung cancer (NSCLC) whose disease has progressed after first-line chemotherapy.[1] However, the failure of chemotherapy does not necessarily imply that antiangiogenesis will fail.[2] Although the disease may have progressed on chemotherapy, vascular endothelial growth factor (VEGF) is a key factor in tumor angiogenesis that is present and stable throughout the tumor life cycle, and it is targeted by bevacizumab. Chemotherapy fails primarily due to disease resistance from genetic instabilities, but antiangiogenic signaling continues throughout the disease lifespan and tumors may still depend on VEGF.

Preclinical studies suggest that continued VEGF inhibition is essential to prevent tumor revascularization or neovascularization.[3] In patients with previously untreated advanced NSCLC, survival was improved by combining bevacizumab with carboplatin and paclitaxel induction treatment over induction treatment alone.[4] The duration of treatment with bevacizumab contributes to its efficacy in patients with metastatic colorectal cancer and ovarian cancer.[5-9] A survival benefit has been associated with continuing bevacizumab after induction-phase therapy in advanced NSCLC in retrospective analyses,[8,9] but this had not been examined in a randomized trial. Among patients with bevacizumab-naïve, advanced NSCLC, a trend toward improved progression-free survival (PFS) occurred with second-line treatment with bevacizumab plus chemotherapy compared with second-line chemotherapy alone.[10]

AvaALL is an ongoing, multinational, open-label, randomized, phase III study that is enrolling patients whose disease has progressed on single-agent maintenance bevacizumab.[11] The study seeks to compare clinical outcomes for patients with advanced NSCLC receiving standard-of-care treatment with or without bevacizumab across treatment lines.

The primary endpoint of the study is overall survival (OS), which is defined as the time from the date of randomization to the date of death from any cause. The secondary endpoints include the OS rates at 6, 12, and 18 months; PFS and time to progression from randomization at first progressive disease (PD1) to second PD (PD2) and to third PD (PD3); response rates, disease control rates, and duration of response at PD2 and PD3; efficacy in patients in the adenocarcinoma histology subgroup; and safety of bevacizumab across multiple treatment lines. The exploratory endpoints are comparative efficacy of bevacizumab in Asian and non-Asian patients, quality of life through multiple treatment lines, and correlation of specimen biomarkers with efficacy and safety outcomes.

The key inclusion criteria is NSCLC with PD after first-line treatment with 4 to 6 cycles of bevacizumab plus platinum doublet-containing monotherapy prior to PD1. Patients can have an interruption of no more than 2 consecutive cycles (42 days) of bevacizumab treatment between the cessation of their first-line treatment and the first day of their second-line treatment. In addition,

patients need to have at least 1 measurable lesion and a performance status (PS) of 0, 1, or 2. Patients with asymptomatic, treated brain metastases are eligible. Patients are excluded if they have mixed non–small cell and small cell tumors or mixed adenosquamous carcinomas with a predominant squamous component; if their disease tests positive for an epidermal growth factor receptor (EGFR) mutation, although EGFR testing is not required; if they have a history of grade 2 or higher hemoptysis (≥2.5 mL of bright red blood) that occurred in the 3 months before randomization; if evidence indicates the tumor is invading a major blood vessel upon imaging; and if radiotherapy to any site was received in the 28 days before randomization, although palliative radiotherapy to bone lesions occurring 14 days or less before randomization is allowed. A protocol amendment to exclude patients with anaplastic lymphoma tyrosine kinase–positive disease is under consideration.

The study is designed to randomize patients in a 1 to 1 manner to second-line standard-of-care therapy with or without bevacizumab. The randomization occurs upon disease progression after first-line bevacizumab plus platinum-doublet induction followed by bevacizumab maintenance treatment. The treatments for second-line standard-of-care include erlotinib, docetaxel, and pemetrexed, with the choice being made by the investigator. The bevacizumab dosage remains the same as the dosage used in the first-line therapy, either 7.5 mg/kg or 15 mg/kg every 3 weeks. The study does not allow any crossover of bevacizumab at any time.

Stratification factors include the type of planned, second-line, standard-of-care treatment (erlotinib vs docetaxel vs pemetrexed), by the number of cycles of bevacizumab maintenance treatment (≤6 vs >6), and by smoking status (never vs former vs current). The study assumes a median OS of 7.9 months (1-year OS rate of 35%) for the control arm and 10.1 months (1-year OS rate of 44%) for the treatment arm (hazard ratio [HR], 0.78) with 1 interim efficacy analysis. The study requires a total of 528 events to achieve 80% power for the log-rank test at a 2-sided significance level of 5%, which means 293 patients are needed for each arm of the study.

The study will ensure the safety and tolerability of the trial regimen through an independent data monitoring committee, and interim safety and efficacy analyses will be performed. The study will enroll approximately 600 patients at 140 study centers in 19 countries. Accrual began in June 2011.

SWOG S0533: A Pilot Trial of Cisplatin (C)/Etoposide (E)/Radiotherapy (RT) Followed by Consolidation Docetaxel (D) and Bevacizumab (B) (NSC-704865) in Three Cohorts of Patients (pts) With Inoperable Locally Advanced Stage III Non-Small Cell Lung Cancer (NSCLC)

Since combining bevacizumab with chemotherapy has improved survival in advanced NSCLC, this trial sought to determine if bevacizumab could be incorporated into standard chemotherapy and radiotherapy for locally advanced NSCLC (Abstract 7018). Bevacizumab was not successfully integrated into chemoradiation for stage III NSCLC, especially for patients at high risk for hemoptysis. Toxicities related to bevacizumab caused several temporary closures that contributed to slow accrual. A total of 29 patients were recruited who had unresectable stage III NSCLC, PS 0 or 1, and adequate organ function. The patients were stratified as either low risk (17 patients) or high risk (12 patients) based on squamous histology, hemoptysis, and tumor with cavitation or near a major vessel. Grade 3 or 4 toxicities during chemoradiotherapy included neutropenia in 10 patients, thrombocytopenia in 2, anemia in 2, febrile neutropenia in 3, esophagitis in 2, and pneumonitis in 1. During the consolidation of docetaxel and bevacizumab, 2 patients with grade 3 pneumonitis and 2 episodes of fatal hemoptysis led to the closure of the high-risk group. Poor accrual led to the closure of the low-risk group. The median OS was 23 months for the low-risk patients and 17 months for the high-risk patients. The data were insufficient to determine safety or efficacy.

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LUX-Lung 3: A Randomized, Open-Label, Phase III Study of Afatinib Versus Pemetrexed and Cisplatin as First-Line Treatment for Patients With Advanced Adenocarcinoma of the Lung Harboring EGFR-Activating Mutations

James C. Yang, MD, presented the LUX-Lung 3 study, which is a randomized, open-label, phase III trial of afatinib versus cisplatin and pemetrexed as first-line treatment for patients with advanced adenocarcinoma of the lung harboring mutations that activate the EGFR.[1] Afatinib is an irreversible ErbB family blocker.[2] Afatinib differs from the reversible EGFR tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib in that after it enters the cell, it covalently binds to the cysteine residue of EGFR. This provides long inhibition of EGFR. Afatinib also inhibits other ErbB family receptor heterodimers, such as human epidermal growth factor receptor (HER) 2, HER3, and HER4. Additionally, afatinib has in vitro activity against the EGFR-resistant T790M mutation.

EGFR mutations define a specific group of patients with exquisite sensitivity to EGFR TKIs, based on 5 prior randomized studies.[3-7] Gefitinib and erlotinib have been compared with combination chemotherapy in phase III randomized studies, and the TKIs have shown better PFS. However, cisplatin and pemetrexed, which is a highly effective and well-tolerated first-line chemotherapy treatment for advanced stage lung adenocarcinoma, was not tested in all of these 5 randomized studies. Afatinib had very good efficacy in lung adenocarcinoma patients with EGFR mutations in the LUX-Lung 2 phase II study.[8] In that study, 61 patients received afatinib as a first-line treatment, and they had a PFS of 12 months, as determined by independent review. Among patients with the common Del19 and L858R mutations in the study, a PFS time of 13.7 months was reached. Based on the results of the LUX-Lung 2 study, the phase III study was begun.

In the LUX-Lung 3 study, patient tumors were screened for EGFR mutation status with TheraScreen, which can detect 29 types of EGFR mutations using a specific polymerase chain reaction (PCR). Key eligibility criteria were standard for first-line patients, and patients with asymptomatic brain metastases were accepted. After the EGFR mutation status of the patients was verified and after checking all the eligibility criteria, the patients were randomized 2:1, stratified by EGFR mutation status and race as Asian or non-Asian, and assigned to afatinib 40 mg/day until disease progression or to cisplatin and pemetrexed chemotherapy at standard doses for up to 6 cycles. The primary endpoint of this study was PFS by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and independent review. The secondary endpoints included survival time, disease control, duration of response, tumor shrinkage, OS, patient-reported outcome, safety, and hormonal kinetics.

The statistical design required 217 independent events to detect an HR of 0.64, or a median increase in PFS from 7 months for patients who received combination chemotherapy to 11 months for patients who received afatinib at 2-sided 5% significance level with 90% power. A total of 330 patients were planned. Stratified log-rank test and Cox proportional hazard compared PFS times with intent-to-treat (ITT) analysis

A Randomized Discontinuation Phase II Trial of Ridaforolimus in Non-Small Cell Lung Cancer (NSCLC) Patients With KRAS Mutations

Ridaforolimus, an inhibitor of mammalian target of rapamycin (mTOR), was tested for its ability to prolong stable disease relative to available standard treatments for NSCLC (Abstract 7531). The patients in this phase II trial had stage IIIB/IV NSCLC, had received prior chemotherapy, and had mutations in KRAS. Oncogenesis mediated by KRAS is affected by mTOR. A total of 79 patients were treated with oral ridaforolimus 5 days per week for 8 weeks. The patients whose tumor shrinkage was at least 30% stayed on ridaforolimus, while those with at least 20% tumor growth discontinued treatment. Then, the 28 patients with stable disease at 8 weeks were randomized 1:1 to ridaforolimus or placebo. At 8 weeks, the overall response rate (CR and PR) was 1%, based on 1 patient of the 79 (95% confidence interval [CI], 0–7%). The primary endpoint was PFS after randomization. The median PFS was 4 months in the ridaforolimus arm and 2 months in the placebo arm (P=.013; HR, 0.36). The median OS was 18 months in the ridaforolimus arm and 5 months in the placebo arm (HR, 0.46; P=.09). The most common adverse events of grade 3 or higher were fatigue (10%), mucositis and stomatitis (10%), pneumonia (10%), dyspnea (9%), diarrhea (6%), and hyperglycemia (6%).

for all randomized patients. Because patients with the common mutations Del19 and L858R had better responses to EGFR TKIs, subgroup analysis was preplanned for patients with these common mutations.

The study started in August 2009, and the last patient entered in February 2011. The turnaround time for EGFR mutation analysis had a median of 5 days. The primary analysis was completed in February 2012. At that time, the median follow-up was 16.4 months, and 221 independently reviewed progression events had occurred. The study was a global effort that included 133 sites in 25 countries in Asia, Australia, Europe, North America, and South America. A total of 1,269 patients were screened, and over 452 had EGFR mutations. A total of 345 patients were randomized, 230 to the afatinib arm and 115 to the combination of cisplatin and pemetrexed. One patient from the afatinib arm and 4 from the chemotherapy arm did not receive their assigned treatments for various reasons.

At the time of analysis, 64% of the required progression events had happened, 65 patients in the afatinib arm were still receiving their afatinib treatment, and all patients had completed their chemotherapy. The demographics and characteristics of the patients in the study arms were well balanced in their predictive and prognostic factors. The patients were 65% female, and 72% were of East Asian ethnicity. Most (68%) had never smoked. A total of 49% of the patients had Del19 mutations, 40% had L858R, and only 10% had uncommon mutations.

The study met its primary endpoint by showing better PFS in patients who received afatinib. The median PFS was 11.1 months in the afatinib arm and 6.9 months in the chemotherapy arm (Figure 1). The HR was 0.58 (P=.0004). At the 12-month time point, 47% of patients who had received afatinib did not progress, and 22% of patients who had received chemotherapy did not progress. The HR for PFS was less than 1 for most factors examined, including sex, ages above or below 65 years, Asian or non-Asian race, the different EGFR mutations, and smoking status. The exception was an HR of 1.04 for patients who were current or ex-smokers. For patients who smoked less than 15 pack-years or less than 1 year, the HR was 0.54 and significantly favored afatinib. According to investigator assessment, the PFS had an HR of 0.49.

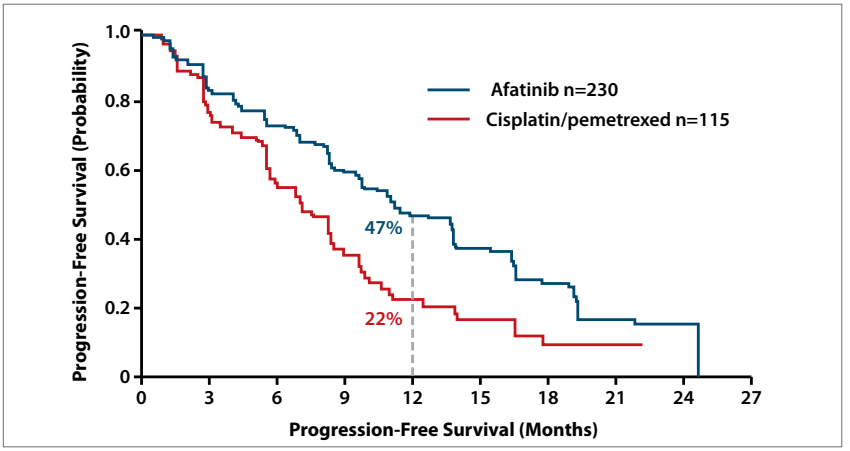

Figure 1. Progression-free survival in the LUX-Lung 3 trial. Data from Yang JC-H et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract LBA7500.

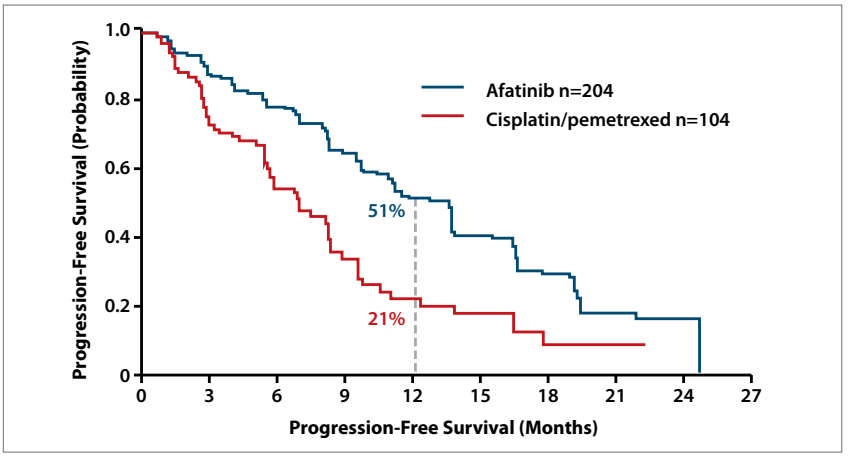

Figure 2. Progression-free survival in the LUX-Lung 3 trial according to epidermal growth factor receptor mutations Del19 or L858R. Data from Yang JC-H et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract LBA7500.

The preplanned analysis of the 308 patients who had the common EGFR mutations Del19 or L858R found that the median PFS was 13.6 months for patients who received afatinib over 1 year, while the median PFS was 6.9 months for those who received chemotherapy (Figure 2). The median PFS for those with the common EGFR mutations in the chemotherapy arm was the same as that in the total population. The HR was 0.47 (P<.0001). At 12 months, 51% of the patients with the common EGFR mutations who received afatinib did not progress, versus 21% of the patients who received chemotherapy.

The patients who received afatinib had better tumor shrinkage and higher objective response (OR; 56% of patients) than those who received chemotherapy

Adjuvant Carboplatin, Docetaxel, Bevacizumab, and Erlotinib Versus Chemotherapy Alone in Patients With Resected Non-Small Cell Lung Cancer: A Randomized Phase II Study of the Sarah Cannon Research Institute (SCRI)

Bevacizumab and erlotinib were safely added to platinum-doublet chemotherapy in the adjuvant setting in this phase II study (Abstract 7035). Patients with resected NSCLC were treated with chemotherapy with bevacizumab that was followed by bevacizumab and erlotinib or by chemotherapy alone. A total of 106 patients who had completely resected (R0) stage IB, II, or IIIA NSCLC; any NSCLC histology; and PS of 0 or 1 were randomized 1:1 to receive 4 cycles of carboplatin, docetaxel, and bevacizumab every 21 days, followed by either 8 cycles of maintenance bevacizumab and erlotinib or 4 cycles of carboplatin and docetaxel every 21 days. For all stages of NSCLC, the 1-year disease-free survival was 78% for patients receiving maintenance bevacizumab and erlotinib, and 88% for those receiving chemotherapy alone (*P*=.66). The 3-year OS for all stages was 81% for those receiving maintenance bevacizumab and erlotinib, and 63% for those receiving chemotherapy alone. The most common grade 3 or 4 hematologic toxicity was neutropenia (18% with maintenance therapy vs 29% with chemotherapy alone). Severe non-hematologic toxicities were fatigue in 6% of patients on maintenance therapy and diarrhea in 6% of patients receiving only chemotherapy. One patient in each arm experienced bronchopleural fistulae, and grade 3 gastrointestinal hemorrhage occurred in 1 patient receiving maintenance therapy.

(22% OR). The differences observed were consistent by investigator assessment and also by common mutations.

All patients experienced adverse events (AEs) with both afatinib and cisplatin, with almost 50% of patients in the study experiencing drug-related AEs of grade 3 or greater. Note that patients who received afatinib had a median follow-up of 16 cycles, while those who received chemotherapy had a median follow-up of only 6 cycles. Only 8% of the patients on the afatinib arm had AEs that led to discontinuation, including 3 patients with suspected lung disease. Among the patients on the chemotherapy arm, 11.7% had AEs that led to discontinuation. During the long follow-up time, 4 patients in the afatinib arm had AEs that led to death and that were considered drug-related by the investigator.

As expected, the most frequent AEs with afatinib treatment were diarrhea, skin rash, stomatitis, paronychia, and dry skin. For patients in the chemotherapy arm, the most frequent AEs were nausea, vomiting, fatigue, and hematologic toxicities. Based on patients' symptoms and questionnaires, the patients receiving afatinib did better with cough, dyspnea, and pain than those receiving chemotherapy, with statistically significant differences for cough and dyspnea. Quality of life was assessed with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire,[9] since quality of life is important when PFS is the primary endpoint. Patients who received afatinib had better global health status and better overall health in all 5 domains detected by the EORTC QLQ-C30.

In summary, LUX-Lung 3 is the largest global prospective trial in EGFR-mutated adenocarcinoma lung cancer, and the first to use cisplatin and pemetrexed as the comparative. LUX-Lung 3 met its primary endpoint of PFS by independent review in the overall study population, as the median PFS was 11.1 months in the afatinib arm and 6.9 months for chemotherapy, with an HR of 0.58. The differences were consistent in all relevant subgroups. Afatinib significantly improved the rate of response and disease control versus chemotherapy. The safety profile of afatinib was consistent with previous phase II studies, as diarrhea and rash were the most frequent AEs. The AEs associated with afatinib were manageable and associated with a low discontinuation rate. First-line afatinib prolonged PFS, delayed the worsening of cancer-related symptoms, and improved the quality of life in patients with EGFR-mutation–positive lung adenocarcinoma.

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SELECT: Randomized Phase III Study of Docetaxel (D) or Pemetrexed (P) With or Without Cetuximab (C) in Recurrent or Progressive Non-Small Cell Lung Cancer (NSCLC) After Platinum-Based Therapy

Edward S. Kim, MD, presented the results of the SELECT (Randomized Phase III Study of Docetaxel [D] or Pemetrexed [P] With or Without Cetuximab [C] in Recurrent or Progressive Non-Small Cell Lung Cancer [NSCLC] After Platinum-Based Therapy) trial, which was a randomized phase III trial of docetaxel or pemetrexed with or without cetuximab in recurrent or progressive NSCLC after platinum-based therapy.[1] Both pemetrexed and docetaxel are approved by the US Food and Drug Administration (FDA) to treat NSCLC after platinum therapy. A single-arm phase II clinical study found interesting efficacy with cetuximab plus docetaxel, as the response rate was 28%.[2] When the SELECT study was being designed, other studies showed the efficacy of adding cetuximab to chemotherapy. One study reported with cisplatin and vinorelbine showed an improved objective response rate of 35% versus 28% in frontline NSCLC.[3] The rationale of the SELECT trial was to combine cetuximab with chemotherapy in the recurrent or progressive NSCLC population.

The study design gave physicians the choice of either pemetrexed or docetaxel as a second-line agent. After that choice, randomization was to single-agent chemotherapy alone versus combination with cetuximab. A maximum of 6 cycles of chemotherapy was administered. The cetuximab was given until toxicity or disease progression.

The primary endpoint was PFS, with the combination of cetuximab with pemetrexed or docetaxel chemotherapy compared with pemetrexed or docetaxel chemotherapy alone.

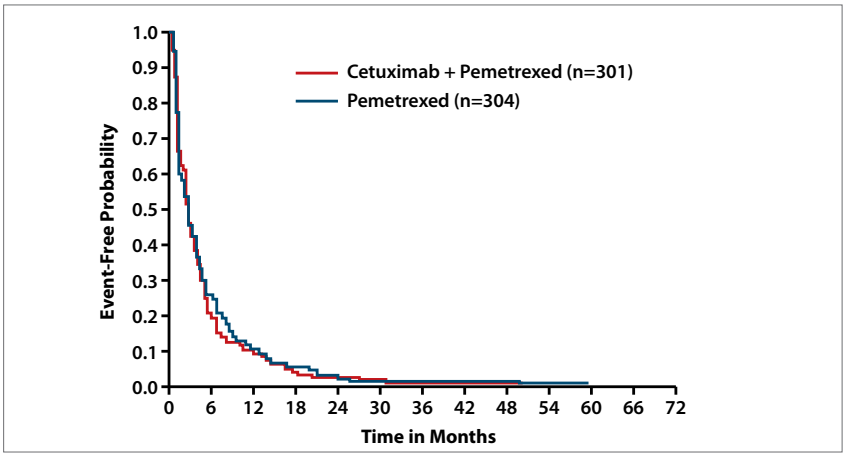

Figure 3. Progession-free survival as assessed by independent review in the SELECT trial. SELECT=Randomized Phase III Study of Docetaxel [D] or Pemetrexed [P] With or Without Cetuximab [C] in Recurrent or Progressive Non-Small Cell Lung Cancer [NSCLC] After Platinum-Based Therapy. Data from Kim ES et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract 7502.

Because of the non-OS endpoint, it was important to have an independent review committee monitor PFS and assess response rates, which were examined as secondary endpoints. These assessments were performed in the whole population and in the chemotherapy arm. The trial was designed to achieve an HR of 0.74, which would include adding cetuximab to increase the median PFS from 2.9 months to 3.9 months. This design required 605 patients in the arms for chemotherapy with or without cetuximab, which would provide a 90% power using the 2-sided log rank test. The analysis was done after 504 events, and stratification factors included prior paclitaxel therapy, time of last platinum dose, PS, and center. The group of 605 patients was the chemotherapy ITT group, and the 2 arms were well balanced, with no significant differences. The predominant pathological diagnosis was nonsquamous. The trial began before the pemetrexed label was changed regarding squamous versus nonsquamous disease.

The reasons for treatment discontinuation were well balanced. Progressive disease was the dominant reason. Patients who finished their 6 cycles of therapy went off the study and were followed. A few patients were described as finishing in the cetuximab plus chemotherapy arm, though cetuximab was given until disease progression.

When the independent review committee assessed the PFS, no statistical difference was seen when cetuximab was added to pemetrexed. The median PFS values were 2.89 months with cetuximab and chemotherapy, compared with 2.76 months with chemotherapy alone (unstratified log-rank P=.7560; Figure 3). The OS values were not statistically different when cetuximab was added

Intrapleural Combination Bevacizumab With Cisplatin Therapy for Non-Small Cell Lung Cancer Caused by Non-Small Cell Lung Cancer

Bevacizumab was effectively and safely used intrapleurally with cisplatin therapy to manage malignant pleural effusion caused by NSCLC (Abstract 7036). This trial enrolled 65 NSCLC patients with malignant pleural effusion. The patients received either intrapleural bevacizumab with cisplatin (n=35) or intrapleural cisplatin (n=30). The group receiving the combination therapy had a curative efficacy of 85.71%, while the cisplatin monotherapy had a curative efficacy of 56.67% ($P<.05$). Additionally, the efficacy of the combination therapy was higher in patients with VEGF-positive cancer ($P<.01$). The combination therapy had good responses in 22 of the 25 cases that had initial resistance to chemotherapy. No severe side effects were detected. The expression of VEGF was reduced by the combination therapy, as measured by quantitative reverse transcription PCR. The authors suggest that the expression level of VEGF can be a prognostic marker for bevacizumab therapy.

to chemotherapy in this second-line population. No complete responses (CRs) occurred in this study of over 900 patients. The partial response (PR) rate was 4.3% in patients receiving chemotherapy alone, and 6.6% in patients receiving cetuximab and chemotherapy ($P=.2000$). These values are largely consistent with available data. For patients whose tissues were available to analyze, EGFR analysis found that the majority of patients were 1+, 2+, and 3+. The EGFR status of about a quarter of the patients could not be determined because of tissue quality or lack of available tissue. When the PFS of the EGFR-positive group was assessed by the independent review committee, no statistical difference was found again between the cetuximab with pemetrexed group versus the pemetrexed alone group. The median PFS times are 3.02 months with cetuximab versus 2.99 months without cetuximab (HR, 1.0165; $P=.8644$). When considering the smaller subset of patients whose EGFR status was undetectable by immunohistochemistry, the PFS times have a small separation, but no statistical difference exists ($P=.6600$). Forest plots that highlight the PFS of the groups and account for histology and EGFR status largely center around the confidence interval.

Among patients who received the median amounts of therapy, the duration of therapy was well balanced among the various subgroups. Dose intensity was very good, highlighting that the regimens were well-tolerated.

More acneiform rash is expected with the EGFR antibody cetuximab, and that was seen. Otherwise, safety results in both arms were largely as anticipated. Pemetrexed is an extremely well tolerated drug in this setting, and the addition of cetuximab did not add any unexpected side effects. Hypomagnesemia, a 6.5% infusion-related reaction, and acneiform rash were expected side effects when cetuximab was combined with pemetrexed.

Analyses of the total group, combining both pemetrexed and docetaxel with or without cetuximab, yielded expected results. The investigator-observed PFS and OS were very similar, with no differences in significance. Forest plots found similar results for PFS and OS for the total group when analyzed by histology and EGFR subgroups. The PFS of patients with undetectable EGFR was an outlier that will be further analyzed, but it was not significant in the overall picture.

In conclusion, adding cetuximab to pemetrexed unfortunately did not improve PFS or OS in this second-line population. Both were well tolerated. Also, no improvements in PFS or OS were seen based on immunohistochemistry or histology differences. The current ongoing analysis, including the H score and the relationship to rash, will be interesting. Kim and colleagues hope that their experience highlights the importance of obtaining analyzable tissue to allow molecular analysis that can define appropriate treatment populations in these types of studies.

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PARAMOUNT: Final Overall Survival (OS) Results of the Phase III Study of Maintenance Pemetrexed (pem) Plus Best Supportive Care (BSC) Versus Placebo (plb) Plus BSC Immediately Following Induction Treatment With Pem Plus Cisplatin (Cis) for Advanced Nonsquamous (NS) Non-Small Cell Lung Cancer (NSCLC)

Luis Paz-Ares, MD, presented the final overall results of 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 [NSCLC]) trial, which involved over 83 centers from 16 countries.[1] This phase III trial examined the role of continuation maintenance with pemetrexed compared with placebo. The patients in the study had already been treated with induction chemotherapy containing cisplatin or pemetrexed for advanced stage, nonsquamous (NS) NSCLC. At the time of diagnosis, most patients have stage IV or grade 3b NSCLC. Pemetrexed has demonstrated efficacy in advanced NS-NSCLC in combination with cisplatin as a first-line doublet,[2] and as a maintenance agent after a non-pemetrexed platinum doublet.[3]

The PARAMOUNT trial evaluated the complementary role of pemetrexed maintenance after induction with pemetrexed and cisplatin. The primary endpoint of PFS was reported at the American Society of Clinical Oncology (ASCO) annual meeting in 2011, and PFS had clear improvement for most patients treated with pemetrexed (HR, 0.62; Wald $P<.0001$).[4] The current presentation centered on the final survival analysis that was scheduled to occur after at least 390 deaths.

The PARAMOUNT trial included only NSCLC patients who had been previously treated, had nonsquamous histology, and had a PS of 0–1. Induction therapy included 4 cycles every 21 days of pemetrexed and cisplatin. After 4 cycles, the patients without progressive disease, who were either responding or had stable disease, were randomized 2 to 1 to continuation maintenance with pemetrexed plus best supportive care (BSC) or to placebo plus BSC. Patients were stratified for PS of 0 versus 1, disease stage at the time of randomization, and response to induction, meaning responding versus stable disease.

The trial enrolled 939 patients. After the induction phase, 400 of the patients were not eligible for randomization into the continuation part of the trial, mainly due to AEs and disease progression. Of the eligible patients, 9 were not randomized: 8 because of patient decision and 1 because of physician decision. A total of 539 patients were randomized, with 359 on the pemetrexed arm and 180 on the placebo arm.

The 2 arms of the study were well balanced, with the patients having a median age of 62 years, more men than women, and about 20% of the patients being never smokers. The patients were 95% Caucasian, as the study was mainly done in Europe. One-third of the patients were PS 0 and two-thirds

GILT Study: Oral Vinorelbine (NVBo) and Cisplatin (P) With Concomitant Radiotherapy (RT) Followed by Either Consolidation (C) With NVBo Plus P Plus Best Supportive Care (BSC) or BSC Alone in Stage (st) III Non-Small Cell Lung Cancer (NSCLC): Final Results of a Phase (ph) III Study

For stage III NSCLC patients, treatment with oral vinorelbine, cisplatin, and concomitant radiotherapy had a high level of efficacy (disease control rate, 86.0%) and low toxicity (Abstract 7001). Consolidation with oral vinorelbine and cisplatin improved the disease control rate in this phase III study. A total of 279 patients received chemotherapy and concomitant radiotherapy, while 201 patients were randomized to receive chemotherapy plus best supportive care (BSC) (n=96) or BSC as consolidation (n=105). The disease control rate among evaluable patients was 86.0% for those receiving chemotherapy and radiation, 84.2% for those receiving chemotherapy and BSC, and 66.3% for those receiving BSC ($P=.0084$). From the time of randomization, the median PFS was 6.4 months for those receiving chemotherapy and BSC versus 5.5 months for those receiving BSC ($P=.63$). No survival advantage for chemotherapy was achieved, as the median OS from the time of randomization was 20.8 months for those receiving chemotherapy and BSC versus 18.5 months for those receiving BSC ($P=.87$). Drug-related toxicity resulted in 3 deaths. The use of oral vinorelbine and cisplatin as consolidation did not enhance lung toxicity.

were PS 1. About 90% of the patients had stage IV adenocarcinoma. The induction responses were partial or complete remission in half the patients and stable disease in the other half.

The final analysis of OS included 397 deaths, which were 71% of the patients treated with pemetrexed and 78% in the placebo arm. Notably, 98% of the patients had already discontinued treatment at the time of the analysis. Each treatment arm had a median of 4 treatment cycles, though the mean was 5 for the placebo arm and nearly 8 for the pemetrexed arm. In other words, 37% of the patients in the pemetrexed arm had at least 6 cycles, compared with 18% of the patients in the placebo arm. The dose intensity was 94%. The trial was mature at the time of analysis, as the median follow-up of the living patients exceeded 24 months.

The main reasons for treatment discontinuation were disease progression and AEs. Progressive disease caused patient discontinuation in 69% of patients in the pemetrexed arm and 84% of patients in the placebo arm. Discontinuation due to AEs was 18% in the pemetrexed arm and 7% in the placebo arm.

The mature OS data indicate that patients in the pemetrexed arm had better OS than those in the placebo arm (unadjusted HR, 0.78; 95% CI, 0.64–0.96; *P*=.0195). The data indicate that 22% of the risk of death was decreased in the pemetrexed arm all along the study observation. The median OS was 13.9 months in the pemetrexed arm and 11.0 months in the placebo arm, which is a 3-month difference (Figure 4). The difference was more pronounced in the second half of the 36-month survival curve. The 2-year survival was 32% for the pemetrexed arm and 21% for the placebo arm. When survival is analyzed from the date of starting induction treatment, the median OS was 16.9 months in the pemetrexed arm and 14.0 months in the placebo arm (HR, 0.78; 95% CI, 0.64–0.96; *P*=.0191; Figure 5).

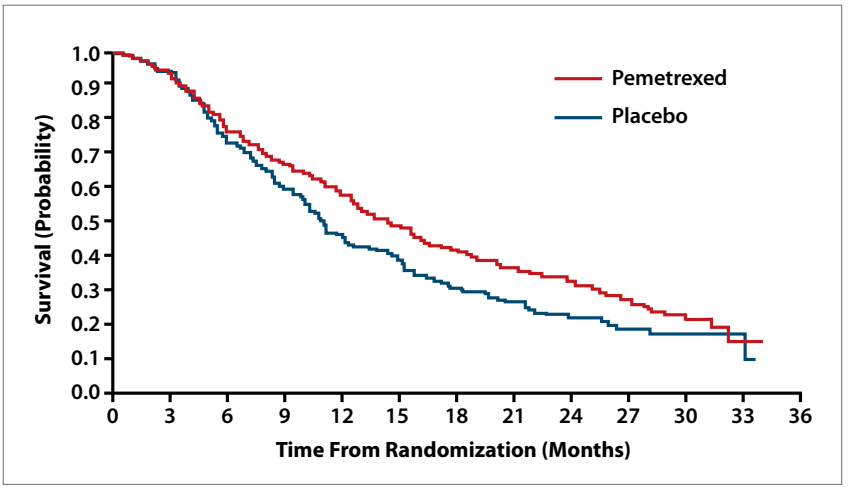

Figure 4. Overall survival from randomization in the PARAMOUNT trial. PARAMOUNT=Phase III Study of Maintenance Pemetrexed [Pem] Plus Best Supportive Care [Bsc] Versus Placebo Plus Bsc Immediately Following Induction Treatment With Pem Plus Cisplatin For Advanced Nonsquamous Non-Small Cell Lung Cancer [NSCLC]). Data from Paz-Ares L et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract LBA7507.

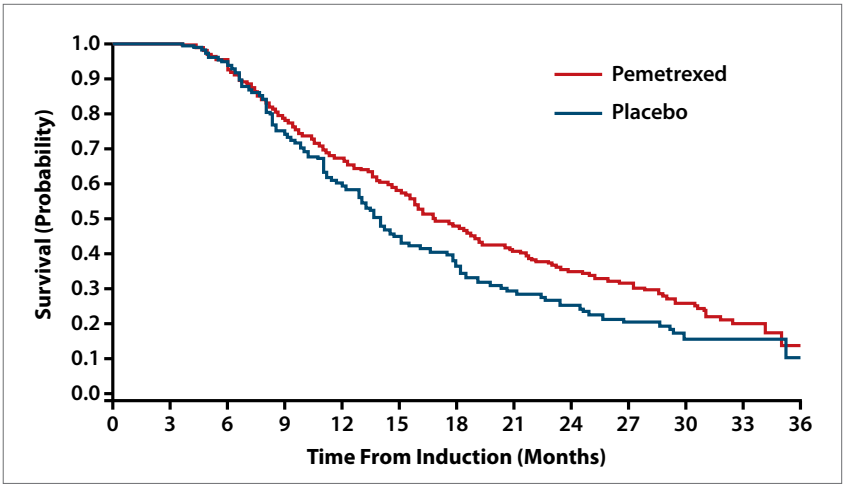

Figure 5. Overall survival from induction in the PARAMOUNT trial. PARAMOUNT=Phase III Study of Maintenance Pemetrexed [Pem] Plus Best Supportive Care [Bsc] Versus Placebo Plus Bsc Immediately Following Induction Treatment With Pem Plus Cisplatin For Advanced Nonsquamous Non-Small Cell Lung Cancer [NSCLC]). Data from Paz-Ares L et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract LBA7507.

Additionally, the PFS values from the 12-month analysis had an HR of 0.62, favoring the pemetrexed arm, which is similar to the PFS values analyzed at the time of final OS (HR, 0.60).

The benefit of treatment was consistent and had a similar magnitude of benefit across all patient subgroups. Patient response to induction treatment produced no difference in the magnitude of benefits. Responding patients with CRs or PRs to induction therapy had an HR of 0.81 favoring pemetrexed, and secondary analysis found the same magnitude of benefit for patients whose best response to induction chemotherapy was stable disease (HR, 0.76).

Discontinuation of treatment is very important for survival. A total of 64% of the patients in the pemetrexed

arm and 72% of the patients in the placebo arm received further treatment. The agents used were not different, with the exception of docetaxel, which was used by 32% of the patients in the pemetrexed arm and 43% of those in the placebo arm.

Toxicity is a relevant issue in maintenance therapy. Grade 3 and 4 toxicities for fatigue, anemia, and neutropenia were between 4% and 6% in the pemetrexed arm, compared with 0–1% in the placebo arm. The pemetrexed arm had higher frequencies of the grade 1 and 2 toxicities of fatigue (17% vs 10%), nausea (13% vs 2%), anemia (11% vs 4%), and vomiting (7.5% vs 1%) than the placebo arm. Note that the patients in the pemetrexed arm received a larger number of cycles than those in the placebo arm.

In conclusion, the final results of the survival analysis of the PARAMOUNT trial show a significant improved outcome for those patients treated with pemetrexed continuation maintenance compared with those treated with placebo (HR, 0.78). The survival benefits were consistent across all the patient subgroups, including the benefit for responding patients compared to those with a stable disease after induction treatment. Dr. Paz-Ares stated his belief that this is the first study to show that continuation maintenance had a clear impact on the natural course of the disease in advanced NSCLC, including an improvement in PFS and OS. This study may support a change in the treatment paradigm in the clinical setting. Dr. Paz-Ares stated that information about the role of maintenance treatment should be shared with patients, although not all patients should be treated this way.

Phase II Study of Pemetrexed (P) Plus Carboplatin (Cb) or Cisplatin (C) With Concurrent Radiation Therapy Followed by Pemetrexed Consolidation in Patients (pts) With Favorable-Prognosis Inoperable Stage IIIA/B Non-Small Cell Lung Cancer (NSCLC)

Inoperable stage IIIA/B NSCLC does not have a consensus chemotherapy regimen with concurrent radiation therapy. This open-label, phase II trial randomized 98 patients with inoperable stage IIIA/B NSCLC of all histologies in a 1 to 1 manner to receive pemetrexed plus carboplatin (n=46) or plus cisplatin (n=52) (Abstract 7002). The therapies were delivered every 21 days for 3 cycles, and every patient received 2 Gy daily for 5 days a week from days 1 through 45. Consolidation pemetrexed was administered every 21 days for 3 cycles that began 3 weeks after the concurrent radiation therapy was completed. The 2-year OS was 45.2% for patients in the carboplatin arm and 57.6% for patients in the cisplatin arm (*P*=.270). The median time to progression was 8.8 months for the carboplatin arm and 13.1 months for the cisplatin arm (*P*=.057). Grade 4 treatment-related AEs were anemia (0% in the carboplatin arm vs 1.9% in the cisplatin arm), neutropenia (6.5% vs 3.8%, respectively), thrombocytopenia (4.3% vs 1.9%, respectively), and esophagitis (0% vs 1.9%, respectively). No deaths related to the treatments were reported. The cisplatin arm may have advantages in OS and time to progression, although conclusions are limited by the size of the study. Pemetrexed combined with either carboplatin or cisplatin appears well tolerated.

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Phase II Double-Blind, Randomized Study of Selumetinib (SEL) Plus Docetaxel (DOC) Versus DOC Plus Placebo as Second-Line Treatment for Advanced *KRAS* Mutant Non-Small Cell Lung Cancer (NSCLC)

Pasi A. Janne, MD, PhD, presented the results of a phase II, double-blind, randomized study of selumetinib and docetaxel versus placebo and docetaxel as second-line treatment for advanced *KRAS*-mutant NSCLC.[1] *KRAS* is the most frequently mutated oncogene in NSCLC outside of Asia, with mutations occurring in 20% of tumors.[2] The effectiveness of chemotherapy may be reduced in this subset of lung cancer patients.[3,4] The NSCLC patients with *KRAS* mutations do not respond to EGFR-targeted therapies.[5] Most importantly, no targeted therapies are currently available for this subpopulation of lung cancer patients.

Selumetinib is a potent and selective allosteric inhibitor of both MEK1 and MEK2.[6] In RAS signaling, MEK is a critical downstream effector protein of *KRAS* signaling. In preclinical studies, cell lines with *KRAS* mutations were more sensitive to selumetinib than cell lines without *KRAS* mutations.[7] When selumetinib was evaluated as a monotherapy in a randomized phase II trial, it had clinical activity in second-line and third-line NSCLC, but selumetinib was not superior to pemetrexed.[8] Patients receiving selumetinib had a PFS of 67 days and a response rate of 5%, while those receiving pemetrexed had a PFS of 90 days and a response rate of 5%. A phase I trial combining selumetinib and docetaxel demonstrated a manageable tolerability profile.[9] A preclinical study found that the combination of docetaxel and selumetinib led to tumor regressions in a *KRAS*-mutant colon cancer model, while only tumor stasis was observed with single-agent selumetinib or docetaxel.[10]

This prospective, phase II, double-blind, placebo-controlled study was designed as a second-line lung cancer trial for patients who had failed first-line, platinum-based chemotherapy. Patients had to have local advanced or metastatic NSCLC with a confirmed *KRAS* mutation and a PS of 0 or 1. Patients were randomized 1:1 to treatment with selumetinib and docetaxel or with placebo and docetaxel. Docetaxel was administered every 21 days, and selumetinib or placebo was administered daily. The number of docetaxel cycles was not predefined, but was based on local practices and investigator preference.

The primary endpoint was OS. Secondary endpoints included PFS, overall response rate, duration of response, change in tumor size, alive and progression-free at 6 months, safety, and tolerability. Notably, after patient enrollments were completed, the primary endpoint was changed from PFS to OS without changing the sample size. This change was to allow decisions to be made based on OS, without breaking the study blinding at an earlier endpoint of PFS. The analysis of OS was planned after 58 events, which would give an HR of 0.57 with 80% power assuming a one-sided 10% significance level.

A total of 422 patients were screened from 67 centers in 12 countries worldwide, and 87 of these patients were randomized, with 44 on the selumetinib and docetaxel arm and 43 on the placebo and docetaxel arm. After randomization, 1 patient from the selumetinib arm and 3 from the placebo arm were excluded because their tumor samples could not be confirmed as positive for *KRAS* mutations.

Patient characteristics were relatively well balanced. Nearly all patients were either former or current smokers, as expected of patients with *KRAS*-mutant NSCLC. The selumetinib arm has a slight imbalance of more stage 3b patients than the placebo arm. The PS 0 and 1 patients were equally distributed. Most patients had adenocarcinoma histology. Notably, the trial

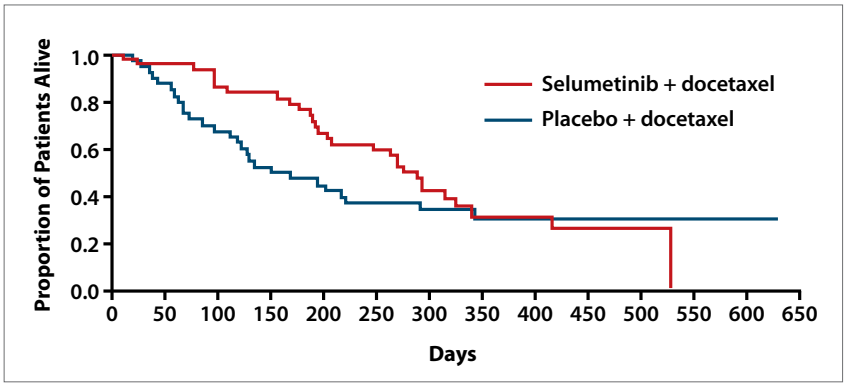

Figure 6. Overall survival in a phase II, double-blind, randomized study of selumetinib and docetaxel versus placebo and docetaxel as second-line treatment for advanced *KRAS*-mutant non–small cell lung cancer. Data from Janne PA et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract 7503.

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%)].

In Study 5, 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 7. The overall incidence of proteinuria (all grades) was only adequately assessed in Study 7, 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 7). [See *Warnings and Precautions (5.8).*]

Congestive Heart Failure (CHF)

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 metastatic breast cancer (MBC), an indication for which Avastin is not approved, the incidence of Grade 3–4 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.

In previously untreated patients with diffuse large B-cell lymphoma (DLBCL), an indication for which Avastin is not approved, the incidence of CHF and decline in left-ventricular ejection fraction (LVEF) were signficantly increased in the Avastin plus R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) arm (n=403) compared to the placebo plus R-CHOP arm (n=379); both regimens were given for 6 to 8 cycles. At the completion of R-CHOP therapy, the incidence of CHF was 10.9% in the Avastin plus R-CHOP arm compared to 5.0% in the R-CHOP alone arm [relative risk (95% CI) of 2.2 (1.3, 3.7)]. The incidence of a LVEF event, defined as a decline from baseline of 20% or more in LVEF or a decline from baseline of 10% or more to a LVEF value of less than 50%, was also increased in the Avastin plus R-CHOP arm (10.4%) compared to the R-CHOP alone arm (5.0%). Time to onset of left-ventricular dysfunction or CHF was 1-6 months after initiation of therapy in at least 85% of the patients and was resolved in 62% of the patients experiencing CHF in the Avastin arm compared to 82% in the control arm.

Ovarian Failure

The incidence of new cases of ovarian failure (defined as amenorrhoea lasting 3 or more months, FSH level ≥ 30 mIU/mL and a negative serum β-HCG pregnancy test) was prospectively evaluated in a subset of 179 women receiving mFOLFOX chemotherapy alone (n = 84) or with Avastin (n = 95). New cases of ovarian failure were identified in 34% (32/95) of women receiving Avastin in combination with chemotherapy compared with 2% (2/84) of women receiving chemotherapy alone [relative risk of 14 (95% CI 4, 53)]. After discontinuation of Avastin treatment, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% (7/32) of the Avastin-treated women. Recovery of ovarian function is defined as resumption of menses, a positive serum β-HCG pregnancy test, or a FSH level < 30 mIU/mL during the post-treatment period. Long term effects of Avastin exposure on fertility are unknown. [See *Warnings and Precautions (5.10), Use in Specific Populations (8.6).*]

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.

AVASTIN® (bevacizumab)

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%).

Glioblastoma

All adverse events were collected in 163 patients enrolled in Study 5 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 7. 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 3.

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Table 3
NCI-CTC Grades 1–5 Adverse Events in Study 7
(Occurring 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 3: 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 (from unapproved intravitreal use for treatment of various ocular disorders): Permanent loss of vision; Endophthalmitis (infectious and sterile); Intraocular inflammation; Retinal detachment; Increased intraocular pressure; Hemorrhage including conjunctival, vitreous hemorrhage or retinal hemorrhage; Vitreous floaters; Ocular hyperemia; Ocular pain or discomfort

Gastrointestinal: Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration

Hemic and lymphatic: Pancytopenia

Hepatobiliary disorders: Gallbladder perforation

Musculoskeletal: Osteonecrosis of the jaw

Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)

Respiratory: Nasal septum perforation, dysphonia

Systemic Events (from unapproved intravitreal use for treatment of various ocular disorders): Arterial thromboembolic events, Hypertension, Gastrointestinal perforation, Hemorrhage

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 7, 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 adequate or well controlled studies of bevacizumab in pregnant women. While it is not known if bevacizumab crosses the placenta, human IgG is known to cross the placenta Reproduction studies in rabbits treated with approximately 1 to 12 times the recommended human dose of bevacizumab demonstrated 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).*

Because of the observed teratogenic effects of bevacizumab in animals and of other inhibitors of angiogenesis in humans, bevacizumab should be used during pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus.

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8.3 Nursing Mothers

It is not known whether Avastin is secreted in human milk. Human IgG is excreted in human milk, but 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).*]

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).*]

8.6 Females of Reproductive Potential

Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin. Long term effects of Avastin exposure on fertility are unknown.

In a prospectively designed substudy of 179 premenopausal women randomized to receive chemotherapy with or without Avastin, the incidence of ovarian failure was higher in the Avastin arm (34%) compared to the control arm (2%). After discontinuation of Avastin and chemotherapy, recovery of ovarian function occurred in 22% (7/32) of these Avastin-treated patients. [See *Warnings and Precautions (5.10), Adverse Reactions (6.1).*]

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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10127309
Initial U.S.Approval: February 2004
Code Revision Date: May 2012

had no essential pathology review, and histological determination was based on local pathology evaluation and review. The most common *KRAS* mutation in this trial was G12C, followed by G12D, and then by G12V, in agreement with a study of the most common *KRAS* mutations in lung adenocarcinoma.[11]

The median number of docetaxel cycles was 5 for patients treated with selumetinib and 4 for those treated with placebo. Patients treated with selumetinib had a median of 117 days of treatment, while those receiving placebo had a median of 68 days. A larger proportion of the patients on the selumetinib arm received 4, 5, or 6 cycles of docetaxel than those on the placebo arm.

The OS of the patients in the selumetinib arm was 9.4 months, compared with 5.2 months for the patients on the placebo arm (HR, 0.8; 1-sided *P*=.2069; Figure 6). This OS analysis has nonproportional hazards, and data are mature, with 67% maturity. In the selumetinib arm, PFS was 5.3 months, compared with 2.1 in the placebo arm (HR, 0.58; 1-sided *P*=.0138; Figure 7). These PFS data are mature, with 86% maturity.

The selumetinib arm had a response rate of 37%, compared with 0% for the placebo arm (*P*<.0001). All the responses were PRs, and the median duration of response was 182 days. Notably, response assessments were performed with RECIST 1.0. The RECIST 1.1 criteria would have identified 1 responder in the placebo arm who had nonevaluable nontarget lesions.

A total of 37% of the patients in the selumetinib arm were alive and progression-free at 6 months, compared with 15.8% of the patients in the placebo arm (*P*=.0158). At the predetermined endpoint of 12 weeks, the change in tumor size favored the selumetinib arm over the placebo arm (1-sided *P*=.004).

The selumetinib arm had a numerically higher number of serious AEs than the placebo arm. Notably, the 2 study arms had similar numbers of AEs leading to discontinuation.

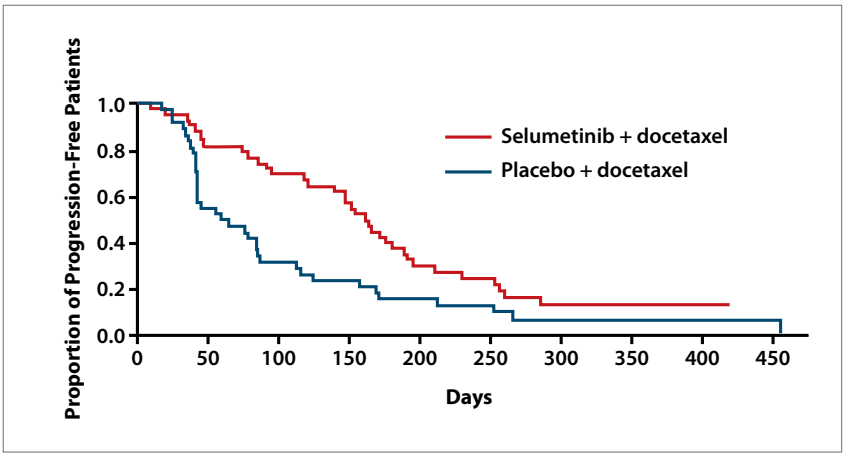

Figure 7. Progression-free survival in a phase II, double-blind, randomized study of selumetinib and docetaxel versus placebo and docetaxel as second-line treatment for advanced *KRAS*-mutant non–small cell lung cancer. Data from Janne PA et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract 7503.

As expected, the patients receiving selumetinib had more AEs leading to dose reduction than the patients receiving placebo. Grade 3 and 4 toxicities had a numerical increase among patients receiving selumetinib compared with those receiving the placebo. The toxicities attributable to selumetinib included diarrhea, nausea, vomiting, peripheral edema, dermatitis acneiform, stomatitis, and the hematological toxicity of febrile neutropenia.

Dr. Janne explained that the trial data raised a concern that docetaxel may have underperformed in this patient population. A previous trial that randomized unselected patients with pemetrexed and docetaxel found a response rate of 8.8%, PFS of 3.5 months, and OS of 7.9 months.[12] Retrospective analyses of patients with *KRAS* mutations who were treated with docetaxel found response rates of 3.7–5%, PFS of 1.5 months, and OS of 4.2 months.[13] These subsets of patients with *KRAS* mutations are small, but the response rate to docetaxel appears to be lower, along with shorter PFS and OS times. Thus, Dr. Janne and colleagues do not believe that docetaxel underperformed in their clinical trial, but they suggest that *KRAS* mutations may identify a subset of patients who do even worse than the general population with docetaxel-based chemotherapy.

In summary, this trial is the first prospective study to demonstrate a clinical benefit for patients with *KRAS*-mutant NSCLC, or even perhaps for *KRAS*-mutant patients of any cancer type. Selumetinib was combined with docetaxel and provided significant improvements in all secondary endpoints, including PFS, response rate, change in tumor size, and alive and progression-free at 6 months. A numerical, but not significant, increase in OS occurred. Tolerability findings were as expected, based on the monotherapy profiles of selumetinib and docetaxel. Further investigations of selumetinib combined with docetaxel and with other chemotherapies are required. Of note, the clinical activity of this combination could be affected by dosing order,[10] and also by loss of such concurrent tumor suppressors as LKB1 and p53. In a recent animal model, cancerous tumors containing both *KRAS* mutations and LKB1 loss did not respond to the combination of selumetinib and docetaxel.[14]

TAILOR: A Phase III Trial Comparing Erlotinib With Docetaxel as the Second-Line Treatment of NSCLC Patients With Wild-Type (wt) EGFR

This phase III trial of NSCLC patients with wild-type EGFR found that PFS with docetaxel was clearly superior to that with erlotinib, an EGFR TKI, for patients with wild-type EGFR (Abstract 7501). A total of 218 evaluable patients with wild-type EGFR at progression who were previously treated with a first-line platinum-based regimen were randomized to receive either erlotinib (n=108) or docetaxel (n=110) until disease progression or unacceptable toxicity. These patients did not have mutations in EGFR exons 19 and 21. The primary endpoint of the study is OS, and the secondary endpoint is PFS. The docetaxel regimen was favored over the erlotinib regimen on the Kaplan-Meier PFS curves (HR, 0.70; 95% CI, 0.53–0.94; *P*=.016). The estimated absolute difference in 6-month PFS was 12% (16% vs 28%), based on the HR. Toxicities were consistent with the literature. The median follow-up was 20 months, and at that point 199 relapses and 157 deaths had occurred. The statistical analysis will require 199 deaths to detect an HR of 0.67 with 2-sided 5% significance level for the log-rank test and a power of 80% to evaluate both OS and PFS. The study authors plan to analyze OS once the planned 199 deaths are reached.

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A Randomized Phase III Trial of Single-Agent Pemetrexed (P) Versus Carboplatin and Pemetrexed (CP) in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) and Performance Status (PS) of 2

Rogerio Lilenbaum, MD, presented results of the randomized phase III trial of single agent pemetrexed versus carboplatin and pemetrexed in patients with advanced NSCLC and PS of 2.[1] He began by explaining that in the CLGB9730 trial reported 10 years ago, a subset of patients with a PS of 2 had a significantly better outcome when treated with carboplatin and paclitaxel compared with paclitaxel alone.[2] Nonetheless, the numbers from that small prospective subset analysis were insufficient to change clinical practice. A subsequent trial compared gemcitabine with carboplatin/gemcitabine in the same patient population, and, though the trial did not reach its target accrual, it did find a high response rate.[3] However, the differences in PFS and OS were not statistically significant. At the 2010 ASCO meeting, Elisabeth Quoix, MD, presented a trial in which elderly patients either received single agent or combination chemotherapy.[4] The survival benefits seen for the combination treatment were maintained in a subset of PS 2 patients, which accounted for more than a quarter of the patients enrolled in the trial. Despite these data, the question of the optimal management of PS 2 patients has remained unresolved.

This study had 2 major objectives. The first objective was to design and conduct a dedicated prospective phase III comparison of the 2 treatment strategies to obtain a definitive answer to an important knowledge gap. The second objective was to develop a research infrastructure that would allow investigators in Brazil to conduct independent, multicentered clinical trials. Although Brazil has had strong participation in global pharmaceutical-sponsored trials, a phase III, multicentered, investigator-initiated trial on lung cancer has never been reported from Brazil or from any other Latin American country. This trial involved 8 centers, and some were more than 2,000 miles apart. The coordinating center was the National Cancer Institute, also known as INCA, in Rio de Janeiro. One center in the United States, in Miami Beach, also participated.

At the time this study was conceived and designed, pemetrexed had not yet been approved for first-line treatment. The interactions between pemetrexed or its efficacy in different histological subtypes had not yet been established. Maintenance treatment was not standard practice, and bevacizumab was just beginning to be used in patients with PS of 0–1. Against this background, the trial was designed. Eligible patients were randomized to either pemetrexed or carboplatin/pemetrexed at standard doses for 4 cycles. All patients received premedication, as directed in the package insert. The stratification factors included stage IIIB versus IV in the old classification, age, and weight loss. The primary endpoint of the trial was OS. Secondary endpoints included PFS, response rate, and safety.

The study was designed to dem-

onstrate an improvement in median survival from 2.9 to 4.3 months, according to Cancer and Leukemia Group B (CALGB) numbers, which required 208 eligible patients. Between April 2008 and July 2011, 217 patients were enrolled, though 12 of them were ineligible and excluded from the analysis. An interim analysis was performed after 46 events, as per protocol. No major safety or efficacy signals were raised at that time. Patients with squamous histology were excluded in a protocol amendment in May 2009. By November 2011, all patients had completed the protocol therapy, and the median follow-up was 6.1 months.

The median age was 65 years in both arms, and approximately one third of the patients were age 70 years and older. The vast majority of the patients had stage IV metastatic disease, and over half of these patients had 5% or greater weight loss. The number of squamous patients had a slight imbalance between the arms, with 11 in the pemetrexed arm and 3 in the combination arm. The imbalance was not statistically significant. Slightly less than 25% of the patients were never smokers. The prevalence of comorbidities, except for mild hypertension, was low. This suggested that the PS 2 of these patients was based primarily on their lung cancer diagnosis and not on comorbidities.

Both arms had a median of 4 cycles delivered, with an identical median dose of carboplatin/pemetrexed. However, a statistically higher percentage of patients in the combination arm completed all 4 cycles of treatment compared with the single-agent arm. This difference was primarily due to a higher rate of discontinuation in the single-agent arm, for reasons of early death, early progression, and clinical degeneration. As expected, therapy delays and dose reductions were more common in the combination arm.

The objective response rate was 10.5% in the pemetrexed arm and 24% in the combination arm (*P*<.029). This was a statistically significant difference, despite the fact that nearly a third of the patients in the single-agent arm and nearly a quarter in the combination arm did not reach the point of a formal response success rate.

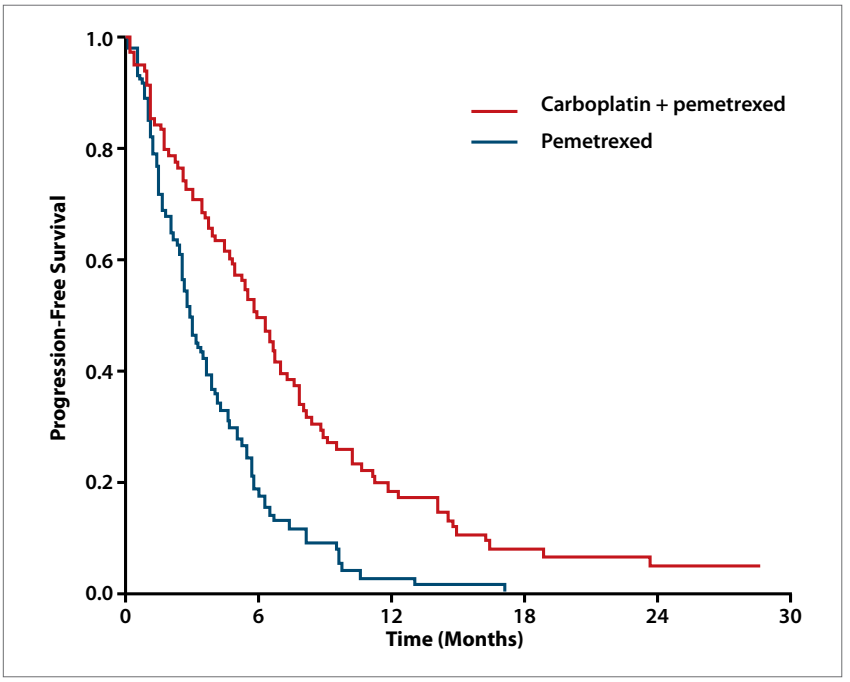

Figure 8. Progression-free survival (PFS) in a randomized phase III trial of single-agent pemetrexed (P) versus carboplatin and pemetrexed (CP) in patients with advanced non–small cell lung cancer and a performance status of 2. Data from Lilenbaum R et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract 7506.

Toxicity was mild, in general. Anemia and neutropenia were more common in the carboplatin-based arm. However, the 2 arms had a similar incidence of febrile neutropenia. Grade 3 and 4 non-hematologic toxicities were notably absent. The dyspnea reported as an adverse event was more likely due to disease and not treatment. A total of 4 documented treatment-related deaths occurred in the combination arm, due to renal failure, sepsis, pneumonia, and thrombocytopenia. Although this is much lower than the rate reported in the study by Quoix and colleagues,[4] it is still higher than what is expected for PS 0–1 patients treated with a carboplatin/pemetrexed regimen.

The combination arm had significantly improved PFS, with the median PFS nearly doubling from 3 to 5.9 months and with the percentage of patients free of progression at 1 year being more than 4-fold higher in the combination arm (Figure 8). The HR was 0.46, representing a 54% reduction in the risk of progression with the use of combination therapy (*P*<.001). Combination therapy also significantly improved OS. The absolute difference in median survival was 3.5 months, from 5.6 to 9.1 months. The 1-year survival rate was more than 2-fold higher in the combination arm. The HR was 0.57 (*P*<.001).

The survival analysis was repeated, excluding patients with squamous cell histology and those with unknown histology. For both PFS and OS, the HRs were nearly identical to the ITT population. When elderly and never-smoker patients were examined as subsets, both subsets had improved OS with the use of combination chemotherapy (elderly, *P*<.015; never smoker, *P*<.035). Despite the small numbers, the difference was highly statistically significant in each subset.

Approximately 30% of the patients received second-line therapy. This is approximately half as many patients with PS 0 to 1 who typically become

candidates for second-line therapy.

In conclusion, combination therapy with carboplatin/pemetrexed significantly improved survival compared to single-agent pemetrexed in patients with advanced NSCLC and a PS of 2. The secondary endpoints of response rate and PFS were also met. The survival benefit was maintained in the subset populations that were studied up to the time of the report. Toxicity was acceptable, even in this high-risk population.

Dr. Lilenbaum stated that these results can be generalized to PS 2 patients with all histological subtypes, provided that they receive the appropriate combination regimen. Though the safety profile of carboplatin/pemetrexed may make it a particularly suitable regimen for this population, the results are not unique to this regimen or to nonsquamous patients. The magnitude of the benefits seen in this study and the unique applicability of the data to clinical practice leads the authors to urge the appropriate organizations to revise their guidelines. Currently, the guidelines still recommend single-agent therapy for these patients. Finally, the research mechanism developed for this trial has served as a model for future investigator-initiated, multicenter trials in Brazil and other Latin American countries.

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Commentary

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Therapeutic decisions in non–small cell lung cancer (NSCLC) are driven by histology and a growing list of actionable genotypes, such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) translocations. At the time of initial biopsy, it is necessary to obtain adequate material for the accurate assessment of histology and molecular testing. The options for patients with nonsquamous carcinoma are much greater than for patients with squamous carcinoma. For many patients, management now involves multiple lines of therapy, whether it is called maintenance or second-line, third-line, or even fourth-line. It is necessary to think critically about how patients are managed to ensure maximum exposure to active agents to increase survival benefits.

Studies Presented at the 2012 ASCO Meeting

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 [NSCLC]) is an important trial that met its primary endpoint of improved progression-free survival (PFS), as reported at the 2011 American Society of Clinical Oncology (ASCO) meeting[1] and in *Lancet Oncology*.[2] Median PFS, measured from randomization, was 4.1 months (95% confidence interval [CI], 3.2–4.6) in the pemetrexed arm and 2.8 months (95% CI, 2.6–3.1) in the placebo arm, as determined by independent assessment.[2] Previous data have shown that the use of pemetrexed as switch maintenance resulted in an improved PFS and overall survival when pemetrexed followed 4 cycles of non-pemetrexed–containing chemotherapy.[3] These data are of limited value, however, because many patients now receive first-line treatment with pemetrexed and cisplatin or carboplatin, a regimen approved in 2008 by the US Food and Drug Administration. The importance of PARAMOUNT is that this trial explored the role of pemetrexed as continuation maintenance rather than switch maintenance.

Overall survival data were presented at the 2012 ASCO meeting.[4] Whether this regimen is referred to as maintenance therapy or as prolonged duration of therapy, the patients who benefit are those with nonprogressive disease throughout the first 4 cycles. Continuation of pemetrexed, which in many patients is well tolerated, can prolong time to progression

and lead to an overall survival advantage, as shown in PARAMOUNT. There was no new toxicity signal in this trial, which provides reassurance that pemetrexed can be used for long durations. In contrast, platinum-based therapy can be hard to tolerate for more than 4 cycles in this setting.

Another first-line agent used in the non-squamous population is bevacizumab. It is administered for 4 cycles, and, if no evidence of progression is found, continued as maintenance therapy. There are a few controversies associated with this regimen. Bevacizumab has not been studied in an isolated manner as a maintenance drug. The mechanism of action of bevacizumab is that of an antiangiogenic drug, and questions have arisen regarding the best approach after the patient progresses, particularly concerning whether continuation of bevacizumab through multiple lines of therapy should be considered. The ongoing AvaALL (A Study of Avastin [Bevacizumab] in Combination With Standard of Care Treatment in Patients With Lung Cancer) trial is evaluating whether continuation of bevacizumab through multiple lines of therapy provides an overall survival benefit in this population.[5] Intriguing data in colon cancer, presented at the 2012 ASCO meeting, suggested that prolonged therapy through multiple lines of bevacizumab has a positive impact.[6] Whether or not benefit will be seen in lung cancer is unknown. Results from AvaALL are eagerly awaited.

LUX-Lung 3 (A Randomized, Open-Label, Phase III Study of Afatinib Versus Pemetrexed and Cisplatin as First-Line Treatment for Patients With Advanced Adenocarcinoma of the Lung Harboring EGFR-Activating Mutations) is an important trial evaluating the new EGFR inhibitor afatinib.[7] Six previous trials—4 of which selected patients based upon genotype—showed that the use of an EGFR tyrosine kinase inhibitor improved outcomes compared to cisplatin-based chemotherapy in patients with EGFR mutations.[8-13] The LUX-Lung 3 trial differs from these previous trials in 2 ways. First, afatinib is a pan–human epidermal growth factor receptor (HER) inhibitor, meaning that it inhibits all of the HER family numbers: HER1, HER2, HER3, and HER4. Afatinib is also an irreversible inhibitor. Second, the LUX-Lung 3 study is the first randomized trial to use a pemetrexed-based chemotherapy as the control arm, which many believe is the preferred agent in adenocarcinoma. In this trial, afatinib was superior to chemotherapy with regard to PFS, response rate, and toxicity rates when used in patients with a known EGFR mutation. The take-home message from LUX-Lung 3 is consistent with the 6 previous EGFR inhibitor trials. Afatinib is another agent that may be available in the future for this population.

The TAILOR (Tarceva Italian Lung Optimization Trial) study compared erlotinib with docetaxel in the second-line setting among patients with wild-type EGFR status.[14] Although approximately 700 patients were registered, only 218 patients were enrolled and evaluable. They were randomized to erlotinib (n=108) or docetaxel (n=110). There was a slight imbalance in the baseline prognostic factors of histology and smoking status between the 2 arms, which is concerning because of the limited number of patients. Although these differences might not be statistically significant, they might be clinically significant. The percentage of former smokers was 10% higher in the docetaxel arm (71.8%) than in the erlotinib arm (81.7%). Another drawback to the study is that patients were not allowed to cross over. For example, patients who received docetaxel in the second-line setting were not permitted to receive erlotinib, even though this agent is approved in the third-line setting. The main concern I have with the TAILOR trial is that the primary endpoint was overall survival, but no data were presented for this outcome. The data showed a higher PFS in favor of docetaxel compared to erlotinib, but PFS was a secondary endpoint. The difference in PFS in this wild-type population was not consistent with previous trials. The toxicities were as expected for both agents. More data from the TAILOR trial must be reported before any assessments of its findings can be made.

The SELECT (Randomized Phase III Study of Docetaxel [D] or Pemetrexed [P] With or Without Cetuximab

Weekly Nab-Paclitaxel in Combination With Carboplatin as First-Line Therapy in Elderly Patients (pts) With Advanced Non-Small Cell Lung Cancer (NSCLC)

Elderly patients with advanced NSCLC are often undertreated. This subgroup analysis of a randomized phase III trial (2010 ASCO Annual Meeting; Abstract LBA7511) evaluated data according to patient age: younger than 70 years and 70 years or older (Abstract 7590). Two treatment regimens were evaluated: nab-paclitaxel plus carboplatin and solvent-based paclitaxel plus carboplatin. In the phase III trial, 15% of patients were ages 70 years or older. In patients of all ages, ORR was higher in the nab-paclitaxel plus carboplatin arm versus the solvent-based paclitaxel plus carboplatin arm (≥70: 34% vs 24%, *P*=.196; <70: 32% vs 25%, *P*=.013). In patients ages 70 years and older, PFS trended in favor of nab-paclitaxel/carboplatin (median, 8.0 vs 6.8 months, HR, 0.687; *P*=.134), and OS was significantly improved (median,19.9 vs 10.4 months, HR, 0.583; *P*=.009). In contrast, among patients younger than 70, PFS and OS were similar in both treatment arms. Adverse events were similar regardless of age. Among the older patients, those in the nab-paclitaxel plus carboplatin arm had less grade 3/4 neutropenia and neuropathy, less pain and hearing loss, and increased thrombocytopenia and anemia as compared with those in the solvent-based paclitaxel plus carboplatin arm.

[C] in Recurrent or Progressive Non-Small Cell Lung Cancer [NSCLC] After Platinum-Based Therapy) study is a randomized phase III trial that compared docetaxel or pemetrexed with or without cetuximab in the second-line setting.[15] The results of this trial were disappointing and support the lack of enthusiasm for the use of cetuximab in unselected patients with NSCLC. However, cetuximab is a monoclonal antibody with a specific target, and there is no reliable biomarker to identify the patient group most likely to benefit from it. In contrast, trastuzumab—a monoclonal antibody that interferes with the HER2/neu receptor—has been evaluated in breast cancer patients with HER2-positive disease. I believe there is a role for cetuximab, but in selected patient subgroups. Some important studies in this area are ongoing. A retrospective analysis of data from the FLEX (A Randomized, Multicenter, Phase III Study of Cetuximab in Combination With Cisplatin/Vinorelbine (CV) Versus CV Alone in the First-Line Treatment of Patients With Advanced Non-Small Cell Lung Cancer [NSCLC]) study using the H-score suggests it is possible to distinguish patients who will achieve greater benefit with cetuximab from those who will not.[16]

An important phase III trial was presented by Rogerio Lilenbaum, MD.[17] This trial randomized patients with a performance status of 2 to carboplatin and pemetrexed versus pemetrexed alone. Most of these patients had a performance status of 2 because they were sick from their cancer. There is still some controversy regarding the optimal approach to patients with this performance status. The study showed a clear, large benefit for the 2-drug strategy. The response rates, including PFS and overall survival, were more than doubled among patients who received carboplatin and pemetrexed. As expected, there was an increase in toxicity with 2 drugs versus 1 drug, including, notably, an increase in treatment-related deaths. However, the magnitude of the benefit was substantial and changes the standard of care in patients with a performance status of 2.

I presented data from a study examining weekly nab-paclitaxel in combination with carboplatin.[18] This subgroup analysis of a phase III trial[19] focused on older patients, who appeared to achieve a significant survival benefit with nab-paclitaxel plus carboplatin as compared with solvent-based paclitaxel and carboplatin in this setting. This subgroup analysis is mostly hypothesis-generating. There are plans for a separate randomized phase II trial with older patients to test the validity of the subanalysis findings.

There were 2 interesting studies in the *KRAS* population, which represents an unmet need. There is no good directed therapy for these patients. There is heterogeneity with regard to the pathways that are activated in the various types of KRAS mutations. The MEK inhibitor selumetinib in combination with docetaxel was compared with docetaxel and a placebo in the second-line treatment of advanced *KRAS*-mutant NSCLC.[20] The combination of selumetinib and docetaxel showed significant improvements in response rates, PFS, and overall survival that were quite noteworthy. It is the first such effect on outcomes seen in the *KRAS*-mutant population and supports further study.

Another study in *KRAS*-mutant patients evaluated ridaforolimus, a mammalian target of rapamycin (mTOR) inhibitor.[21] In this randomized, discontinuation phase II trial, all patients began treatment with ridaforolimus. Those patients who achieved stable disease after 8 weeks of treatment were randomized to continued treatment with ridaforolimus or placebo. Patients who continued therapy with ridaforolimus achieved a significant benefit in PFS and overall survival. These 2 studies provide some optimism in the difficult-to-treat population of *KRAS*-mutant patients. There may be new drugs and new approaches, either single agents or agents used in combination with standard therapies, that may improve outcomes.

A trial from the Southwest Oncology Group (SWOG) found that the incorporation of bevacizumab into a standard platform of chemoradiotherapy was not feasible due to increased toxicities.[22] My colleagues and I recently published a study with a similar outcome.[23] Our results suggest that bevacizumab is a difficult agent to combine with chemoradiation, and this approach should not be taken outside the context of a clinical trial.

Acknowledgment

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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), 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), 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 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 (14.3)*.]

1.4 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 2.6% compared to 0.8% 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).*]

5.10 Ovarian Failure

The incidence of ovarian failure was higher (34% vs. 2%) in premenopausal women receiving Avastin in combination with mFOLFOX chemotherapy as compared to those receiving mFOLFOX chemotherapy alone for adjuvant treatment for colorectal cancer, a use for which Avastin is not approved. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin. [See *Adverse Reactions (6.1), Use in Specific Populations (8.6).*]

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).*]
- Ovarian Failure [See *Warnings and Precautions (5.10), Use in Specific Populations (8.6).*]

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 4198 patients with CRC, non-squamous NSCLC, glioblastoma, or mRCC trials including controlled (Studies 1, 2, 4, and 7) or uncontrolled, single arm (Study 5) treated at the recommended dose and schedule for a median of 8 to 23 doses of Avastin. [See *Clinical Studies (14).*] The population was aged 18-88 years (median 60 years), 43.6% male and 83.8% white. The population included 1783 first- and second-line mCRC patients who received a median of 10 doses of Avastin, 480 first-line metastatic NSCLC patients who 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. These data also reflect exposure to Avastin in 363 patients with metastatic breast cancer (MBC) who received a median of 9.5 doses of Avastin, 669 female adjuvant CRC patients who received a median of 23 doses of Avastin and exposure to Avastin in 403 previously untreated patients with diffuse large B-cell lymphoma (DLBCL) who received a median of 8 doses of Avastin. Avastin is not approved for use in MBC, adjuvant CRC, or DLBCL.

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 5, 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 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, more patients in the Avastin containing arm experienced deep venous thrombosis (34 vs. 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

The risk of developing a second thromboembolic event while on Avastin and oral anticoagulants was evaluated in two randomized studies. 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 (VTE). 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.

In a second, randomized, 4-arm study in 1401 patients with mCRC, prospectively evaluating the incidence of VTE (all grades), the overall incidence of first VTE was higher in the Avastin containing arms (13.5%) than the chemotherapy alone arms (9.6%). Among the 116 patients treated with anticoagulants following an initial VTE event (73 in the Avastin plus chemotherapy arms and 43 in the chemotherapy alone arms), the overall incidence of subsequent VTEs was also higher among the Avastin treated patients (31.5% vs. 25.6%). In this subgroup of patients treated with anticoagulants, the overall incidence of bleeding, the majority of which were Grade 1, was higher in the Avastin treated arms than the chemotherapy arms (27.4% vs. 20.9%). [See *Dosage and Administration (2.4).*]

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%)].

In Study 5, 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 7. The overall incidence of proteinuria (all grades) was only adequately assessed in Study 7, 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 7). [See *Warnings and Precautions (5.8).*]

Congestive Heart Failure (CHF)

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 metastatic breast cancer (MBC), an indication for which Avastin is not approved, the incidence of Grade 3–4 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.

In previously untreated patients with diffuse large B-cell lymphoma (DLBCL), an indication for which Avastin is not approved, the incidence of CHF and decline in left-ventricular ejection fraction (LVEF) were signficantly increased in the Avastin plus R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) arm (n=403) compared to the placebo plus R-CHOP arm (n=379); both regimens were given for 6 to 8 cycles. At the completion of R-CHOP therapy, the incidence of CHF was 10.9% in the Avastin plus R-CHOP arm compared to 5.0% in the R-CHOP alone arm [relative risk (95% CI) of 2.2 (1.3, 3.7)]. The incidence of a LVEF event, defined as a decline from baseline of 20% or more in LVEF or a decline from baseline of 10% or more to a LVEF value of less than 50%, was also increased in the Avastin plus R-CHOP arm (10.4%) compared to the R-CHOP alone arm (5.0%). Time to onset of left-ventricular dysfunction or CHF was 1-6 months after initiation of therapy in at least 85% of the patients and was resolved in 62% of the patients experiencing CHF in the Avastin arm compared to 82% in the control arm.

Ovarian Failure

The incidence of new cases of ovarian failure (defined as amenorrhoea lasting 3 or more months, FSH level ≥ 30 mIU/mL and a negative serum β-HCG pregnancy test) was prospectively evaluated in a subset of 179 women receiving mFOLFOX chemotherapy alone (n = 84) or with Avastin (n = 95). New cases of ovarian failure were identified in 34% (32/95) of women receiving Avastin in combination with chemotherapy compared with 2% (2/84) of women receiving chemotherapy alone [relative risk of 14 (95% CI 4, 53)]. After discontinuation of Avastin treatment, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% (7/32) of the Avastin-treated women. Recovery of ovarian function is defined as resumption of menses, a positive serum β-HCG pregnancy test, or a FSH level < 30 mIU/mL during the post-treatment period. Long term effects of Avastin exposure on fertility are unknown. [See *Warnings and Precautions (5.10), Use in Specific Populations (8.6).*]

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%).

Glioblastoma

All adverse events were collected in 163 patients enrolled in Study 5 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 7. 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 3.

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Table 3
NCI-CTC Grades 1–5 Adverse Events in Study 7
(Occurring 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 3: 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 (from unapproved intravitreal use for treatment of various ocular disorders): Permanent loss of vision; Endophthalmitis (infectious and sterile); Intraocular inflammation; Retinal detachment; Increased intraocular pressure; Hemorrhage including conjunctival, vitreous hemorrhage or retinal hemorrhage; Vitreous floaters; Ocular hyperemia; Ocular pain or discomfort

Gastrointestinal: Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration

Hemic and lymphatic: Pancytopenia

Hepatobiliary disorders: Gallbladder perforation

Musculoskeletal: Osteonecrosis of the jaw

Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)

Respiratory: Nasal septum perforation, dysphonia

Systemic Events (from unapproved intravitreal use for treatment of various ocular disorders): Arterial thromboembolic events, Hypertension, Gastrointestinal perforation, Hemorrhage

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 7, 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 adequate or well controlled studies of bevacizumab in pregnant women. While it is not known if bevacizumab crosses the placenta, human IgG is known to cross the placenta Reproduction studies in rabbits treated with approximately 1 to 12 times the recommended human dose of bevacizumab demonstrated 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)*.]

AVASTIN® (bevacizumab)

Because of the observed teratogenic effects of bevacizumab in animals and of other 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.

8.3 Nursing Mothers

It is not known whether Avastin is secreted in human milk. Human IgG is excreted in human milk, but 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)*.]

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)*.]

8.6 Females of Reproductive Potential

Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin. Long term effects of Avastin exposure on fertility are unknown.

In a prospectively designed substudy of 179 premenopausal women randomized to receive chemotherapy with or without Avastin, the incidence of ovarian failure was higher in the Avastin arm (34%) compared to the control arm (2%). After discontinuation of Avastin and chemotherapy, recovery of ovarian function occurred in 22% (7/32) of these Avastin-treated patients. [See *Warnings and Precautions (5.10), Adverse Reactions (6.1)*.]

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
A Member of the Roche Group

Avastin® (bevacizumab)

Manufactured by:
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A Member of the Roche Group
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94080-4990

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10127309
Initial U.S.Approval: February 2004
Code Revision Date: May 2012

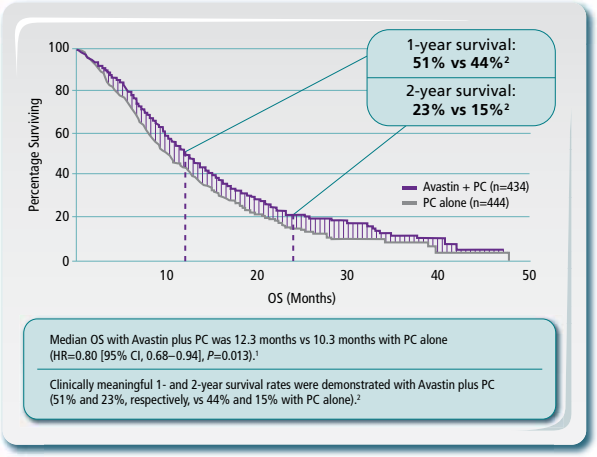
To confront the threat of angiogenesis
in first-line metastatic non-squamous NSCLC…

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

- **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 healing complications 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 adverse events

- Additional serious and sometimes fatal adverse events with increased incidence in the Avastin-treated arm vs control included
  - — Non-GI fistula formation (≤0.3%)
  - — Arterial thromboembolic events (grade ≥3, 2.4%)
  - — Proteinuria including nephrotic syndrome (<1%)
- Additional serious adverse events with increased incidence in the Avastin-treated arm vs control included
  - — Hypertension (grade 3–4, 5%–18%)
  - — 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
- Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin

Most common adverse events

- 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
  - — Exfoliative dermatitis
- Across all studies, Avastin was discontinued in 8.4% to 21% of patients because of adverse reactions

Pregnancy warning

- Avastin may impair fertility
- Based on animal data, Avastin may cause fetal harm
- 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. September 2011.
2. Sandler A, Gray R, Perry MC, et al. *N Engl J Med.* 2006;355:2542-2550.

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