Highlights in NSCLC From the 2012 American Society of Clinical Oncology Annual Meeting  
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Special Reporting on:

• 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

• 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

• 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)

• 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

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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ON THE WEB:  
www.clinicaladvances.com
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 adenocarcinomas 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 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.

References

J. 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 EGFR mutations that activate the EGFR. Afatinib is an irreversible ErbB family blocker. 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. 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. 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.
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 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.

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 (RO) 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.

References

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

Bevacizumab was effectively and safely used intrathecally 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 intrathecal bevacizumab with cisplatin (n=35) or intrathecal 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.

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.

References

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

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. 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 doubler, and as a maintenance agent after a non-pemetrexed platinum doublet.

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). The current presentation centered on the final survival analysis that was scheduled to occur after at least 390 deaths.

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; \(P=0.0195\)). 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; \(P=0.0191\); Figure 5).

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.

References
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. KRAS is the most frequently mutated oncogene in NSCLC outside of Asia, with mutations occurring in 20% of tumors. The effectiveness of chemotherapy may be reduced in this subset of lung cancer patients. 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. In RAS signaling, MEK is a critical downstream effector protein of KRAS signaling. In preclinical studies, cell lines with KRAS mutations do not respond to EGFR-targeted therapies. Most importantly, no targeted therapies are currently available for this subpopulation of lung cancer patients.

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. 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. 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.

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 had 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...
The incidence of Grade 3 or 4 neutropenia was increased in mCRC patients receiving bolus-IFL plus Avastin as compared to the bolus-IFL plus placebo 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 treatment in at least 85% of the patients and was resolved in 62% of the patients experiencing CHF in the Avastin arm compared to 83% in the control arm.

Ovarian failure

The incidence of new cases of ovarian failure (defined as amenorrhea lasting 3 or more months, FSH >10 mIU/mL, and a negative serum β-hCG pregnancy test) was prospectively evaluated in a subset of 179 women receiving mFOLFOX6 chemotherapy alone (n = 48) or with Avastin (n = 90). New cases of ovarian failure were identified in 34% (32/96) of women receiving Avastin in combination with disease (n = 90) compared to 16% (7/48) in those receiving chemotherapy alone (relative risk of 1.95 (95% CI: 1.13, 3.33). After discontinuation of Avastin treatment, the incidence of ovarian failure at all time points after the post-treatment period was documented in 22% (7/32) of the Avastin-treated women. Recovery of ovarian function is defined as resumption of menstruation, a monthly cycle at a FSH level ≤ 30 mIU/mL before the next post-treatment period. Long term effects of Avastin exposure on fertility are unknown. See Warnings and Precautions (5.10). See Use in Specific Populations (8.6).

Metastatic Colorectal Cancer (mCRC)

The data in Table 3 were generated 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 4) adverse events were reported in higher incidence (≥ 2%) in patients receiving belo-IFL plus Avastin compared to belo-IFL plus placebo.

Table 3

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<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 3</th>
<th>Grade 4</th>
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<td>6%</td>
<td>11%</td>
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Cardiovascular:

In patients receiving Avastin or Avastin plus irinotecan (N = 163), the incidence of Grade 3 or 4 neutropenia was increased in mCRC patients compared to patients receiving irinotecan alone (37%). In patients receiving Avastin plus irinotecan, the time to onset of neutropenic infection was 6 or more months, FSH level ≥ 30 mIU/mL and a negative serum of CHF and decline in left-ventricular ejection fraction (LVEF) were occurred at a higher incidence (≥ 3%).

In previously untreated patients with diffuse large B-cell lymphoma (DLBCL), an indication for Avastin is not approved, the incidence of CHF and in left-ventricular ejection fraction (LVEF) were significantly 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 regimes 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 0.3% in patients receiving CHF in the Avastin plus placebo arm (2.2% as compared to the control arm (0.3%). Among patients receiving prior anthracycline chemotherapy, the risk of CHF was 3.8% for patients receiving Avastin as compared to 0.6% for patients receiving placebo as 0.6% for patients receiving paclitaxel/carboplatin (PC) alone.

The incidence of Grade ≥ 3 left ventricular dysfunction was 1.0% in previously untreated patients with metastatic renal cell carcinoma (mRCC) who received Avastin compared to 0.2% in the control arm across the mRCC studies (Study 7). The incidence of Grade ≥ 3 left ventricular dysfunction was 1.0% in previously untreated patients with diffuse large B-cell lymphoma.

In patients receiving Avastin and interferon alfa alone compared to interferon alfa alone.

Cardiovascular:

Hypertension

Grade 4 hypertension (≥ 3%) was reported in 22% (10/46) of patients receiving IFL plus Avastin compared to 2% (1/46) in patients receiving IFL alone (21%). In patients receiving IFL plus Avastin (21%) compared to patients receiving IFL alone (14%). In patients receiving IFL plus Avastin as compared to the bolus-IFL plus placebo 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 treatment at least 85% of the patients and was resolved in 62% of the patients experiencing CHF in the Avastin arm compared to 83% in the control arm.

Ovarian failure

The incidence of new cases of ovarian failure (defined as amenorrhea lasting 3 or more months, FSH >10 mIU/mL, and a negative serum β-hCG pregnancy test) was prospectively evaluated in a subset of 179 women receiving mFOLFOX6 chemotherapy alone (n = 48) or with Avastin (n = 90). New cases of ovarian failure were identified in 34% (32/96) of women receiving Avastin in combination with disease (n = 90) compared to 16% (7/48) in those receiving chemotherapy alone (relative risk of 1.95 (95% CI: 1.13, 3.33). After discontinuation of Avastin treatment, the incidence of ovarian failure at all time points after the post-treatment period was documented in 22% (7/32) of the Avastin-treated women. Recovery of ovarian function is defined as resumption of menstruation, a monthly cycle at a FSH level ≤ 30 mIU/mL before the next post-treatment period. Long term effects of Avastin exposure on fertility are unknown. See Warnings and Precautions (5.10). See Use in Specific Populations (8.6).

Metastatic Colorectal Cancer (mCRC)

The data in Table 3 were generated 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 (hypo...
AVASTIN® (bevacizumab)

8.3 Nursing Mothers

It is not known whether Avastin is excreted 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 also excreted 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 the drug, taking into account the half-life of the bevacizumab (approximately 30 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.

Anti-tumor 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 pilocytic astrocytomas with open growth plates exhibited physical dysplasia following 4 to 26 weeks exposure at 0.4 to 10 times the recommended human dose (based on mg/kg and exposure). The incidence and severity of physical 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 venous thrombosis, hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation, anemia, leukopenia, anemia, dehiscence, 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 (5.10).]

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 dyspnea, gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice alteration.

In an exploratory, pooled analysis of 1745 patients treated in five randomized, controlled trials, 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 (0.5% vs 2.9%) as compared to those <65 years (0.1% vs 1.4%). [See Warnings and Precautions (5.8).]

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% (132) 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) was associated with headache in nine of 10 patients and with severe headache in three of 16 patients.

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=0.069; 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=0.0138; 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<0.0001). 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=0.0158). At the predetermined endpoint of 12 weeks, the change in tumor size favored the selumetinib arm over the placebo arm (1-sided P=0.004).

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.
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 pemtrexed and docetaxel found a response rate of 8.8%, PFS of 3.5 months, and OS of 7.9 months. 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. 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, 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.

References
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 CLGGB9730 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 < 0.029). 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.

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 < 0.001). 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 < 0.001).

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 < 0.015; never smoker, P < 0.035). 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.

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 and in Lancet Oncology. 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. 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. 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. 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.

References

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.3 Intriguing data in colon cancer, presented at the 2012 ASCO meeting, suggested that prolonged therapy through multiple lines of bevacizumab has a positive impact.4 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.5 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.6,8,13 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...
tial 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.\textsuperscript{18} This subgroup analysis of a phase III trial\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{22} My colleagues and I recently published a study with a similar outcome.\textsuperscript{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
Dr. Socinski has no real or apparent conflicts of interest to report.

References


were evaluated with serial CNS imaging, significant Grade 2 CNS hemorrhage was documented in one of 83 Avastin-treated patients (1.2%).

Intracranial hemorrhage occurred in 8 of 163 patients with previously treated metastatic disease. Two events 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 hemoptysis of ≥ 1 teaspoon of red blood.

5.4 Non-Gastrointestinal Fistula Formation

Serious and sometimes fatal non-gastrointestinal fistula formation involving tracheo-oesophageal, bronchopleural, biliary, vaginal, renal and biliary 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 treatment.

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

5.5 Arterial Thromboembolic Events

Serious and sometimes fatal arterial thromboembolic events (AITE) including cerebral infarction, transient ischemic attack, myocardial infarction, angioplasty, and a variety of other AITE occurred at a higher incidence in patients receiving Avastin compared to those in the control arm. Across indications, the incidence of Grade ≥ 3 AITE 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 AITE 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 AITE has not been studied. Discontinue Avastin in patients who experience a severe AITE. [See Dosage and Administration (2.4)].

5.6 Hypertension

The incidence of severe hypertension is increased in patients receiving Avastin compared to controls. Across clinical studies the incidence of Grade ≥ 3 hypertension was 8.4% compared to 2.0% in controls. Monitor blood pressure every two to three weeks during treatment with Avastin as compared to controls. Across clinical studies the incidence of Grade ≥ 3 hypertension was 8.4% compared to 2.0% in controls. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. [See Use in Specific Populations (8.6)].

The most common adverse reactions observed in patients at a rate > 10% and at least twice the rate in controls were headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lassitude disorder, back pain and exfoliative dermatitis. Across all studies, ATE was sustained or 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 the 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, 7) and/or uncontrolled, single arm (Study 5) treated at the recommended dose of Avastin (5 mg/kg). Across all studies, Avastin was discontinued in 8.4% of patients (5.6% for patients with NSCLC, 2.8% for patients with glioblastoma, and 10.8% for patients with mRCC).

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

5.6 Hypertension

The incidence of severe hypertension is increased in patients receiving Avastin compared to controls. Across clinical studies the incidence of Grade ≥ 3 hypertension was 8.4% compared to 2.0% in controls. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. [See Use in Specific Populations (8.6)].

The most common adverse reactions observed in patients at a rate > 10% and at least twice the rate in controls were headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lassitude disorder, back pain and exfoliative dermatitis. Across all studies, ATE was sustained or discontinued in 8.4 to 21% of patients because of adverse reactions.

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Dry Mouth 2% 7% 4%

Weight Loss 10% 15% 16%

Thrombocytopenia 0% 5% 5%

Body as a Whole:

Proteinuria 20% 32% 30%

Cardiovascular:

Arterial thromboembolic events, Hypertension, Pulmonary hypertension, RPLS, Mesenteric venous occlusion

Renal:

Renal thrombotic microangiopathy (manifested as severe proteinuria)

Osteonecrosis of the jaw

General disorders and administration

Nausea, vomiting, dry mouth, constipation, diarrhea, abdominal pain

Dyspepsia

Diabetes mellitus

Liver function tests, increased

Taste alteration

Proteinuria

Hypertension

Vomiting

Anorexia

Constipation

Stomatitis

Bleeding

Vital signs

Nervous:

Dizziness

Musculoskeletal and connective tissue disorders

Epilepsy

Voice alteration

Skin:

Fingernail changes

Hypertrichosis

Hair color change

Skin fold thickening

Skin changes

Angioedema

Skin and appendages

Hair color change

Vision disturbances

Otherophthalmic disorders:

Ocular inflammation, Blurred vision

Adverse events were recorded 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/or represented in table 3:

ovarian bleeding (4 patients vs. 1 patient); amenorrhea (2 patients vs. 1 patient); breast pain (2 patients vs. 1 patient); dyspareunia (2 patients vs. 1 patient)

Adverse events with a frequency of 1% or greater in patients receiving Avastin plus irinotecan are listed in table 4.

14.5% (n = 337). The effect of Avastin on overall survival was similar in elderly patients as compared to younger patients.

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

Think Avastin

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

| Additional serious adverse events with increased incidence in the Avastin-treated arm vs control included |
| Hypertension (grade 3-4, 5%–18%) | Proteinuria including nephrotic syndrome (≤0.3%) |
| Reversible posterior leukoencephalopathy syndrome (RPLS) (≤0.1%) | Arterial thromboembolic events (grade ≥3, 2.4%) |
| 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 —  Proteinuria —  Lacrimation disorder
  - Headache —  Taste alteration —  Back pain
  - Hypertension —  Dry skin —  Exfoliative dermatitis
  - Rhinitis —  Rectal hemorrhage

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%), hypernatremia (4% vs 1%), headache (3% vs 1%), and proteinuria (3% vs 0%)

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%)

References: