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A SPECIAL MEETING REVIEW EDITION

Highlights in NSCLC From the 15th World Conference on Lung Cancer

A Review of Selected Presentations From the 15th World Conference on Lung Cancer • October 27-31, 2013 • Sydney, Australia

Special Reporting on:

- An Intergroup Randomized Phase III Comparison of Standard-Dose (60 Gy) Vs High-Dose (74 Gy) Chemoradiotherapy (CRT) +/- Cetuximab (cetux) for Stage III Non-Small Cell Lung Cancer (NSCLC): Results on Cetux From RTOG 0617
- Efficacy and Safety of Paclitaxel and Carboplatin With Bevacizumab for the First-Line Treatment of Patients With Nonsquamous Non-Small Cell Lung Cancer (NSCLC): Analyses Based on Age in the Phase 3 PointBreak and E4599 Trials
- Value of Adding Erlotinib to Thoracic Radiation Therapy With Chemotherapy for Stage III Non-Small Cell Lung Cancer: A Prospective Phase II Study
- Bevacizumab and Erlotinib or Bevacizumab, Cisplatin and Pemetrexed in Patients With Metastatic Non-Small Cell Lung Cancer: EGFR Mutation Based Treatment Allocation and Repeat Biopsy at Progression in the SAKK19/09 (BIOPRO) Trial
- Clinical Trials of PD-1 and PD-L1 Inhibitors in NSCLC

PLUS Meeting Abstract Summaries

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PL03.05 An Intergroup Randomized Phase III Comparison of Standard-Dose (60 Gy) Vs High-Dose (74 Gy) Chemoradiotherapy (CRT) +/- Cetuximab (cetux) for Stage III Non-Small Cell Lung Cancer (NSCLC): Results on Cetux From RTOG 0617

A decade ago, the standard of care for unresectable stage III non–small cell lung cancer (NSCLC) was a combination of chemotherapy and radiation at a dose of approximately 60 Gy. Phase 1 and phase 2 trials from the Radiation Therapy Oncology Group (RTOG) and others showed that radiation doses as high as 74 Gy could be delivered safely with chemotherapy and might improve both locoregional control and overall survival (OS).[1] A retrospective review and secondary analysis of RTOG trial data suggested that escalating the dose of radiation might improve outcomes. In addition, cetuximab, a monoclonal antibody to the epidermal growth factor receptor (EGFR), has shown efficacy when combined with chemotherapy in stage IV disease. In the RTOG 0324 trial of patients with stage III NSCLC, cetuximab added to chemoradiation yielded a 49% 2-year OS and a median OS of 22.7 months.[2]

Based on these findings, the design of the phase 3 RTOG 0617 study, which compared standard-dose radiation vs high-dose radiation combined with concurrent carboplatin and paclitaxel, was amended to include the addition of cetuximab.[3] The study was originally designed to determine the superior radiation dose. However, after the first 79 patients were randomized, encouraging results emerged from RTOG 0324, and a second randomization was added to evaluate the role of cetuximab. Therefore, there were 2 primary objectives of RTOG 0617. The first was to compare differences in OS between 2 doses of radiotherapy, 60 Gy and 74 Gy, given in combination with concurrent chemotherapy. The second primary objective was to identify whether the addition of cetuximab to chemoradiation improves OS compared with chemoradiation alone.

Patients were randomized to 1 of 4 arms and stratified according to radiation technique, performance status [PS], positron emission tomography staging, and histology. Patients in arm A underwent concurrent chemotherapy and radiation, with a standard total radiation dose of 60 Gy given 5 times per week for 6 weeks. Concurrent chemotherapy included weekly carboplatin (area under the curve [AUC], 2) and paclitaxel (45 mg/m^2) followed by 2 cycles of consolidation chemotherapy (carboplatin [AUC, 6] plus paclitaxel [200 mg/m^2] once every 3 weeks). Patients in arm B received radiation to a total dose of 74 Gy plus the same concurrent chemotherapy. Patients in arm C were treated with standard-dose radiation and concurrent chemotherapy with the addition of weekly cetuximab (400 mg/m^2 loading dose plus 250 mg/m^2), which was continued through the 2 cycles of consolidation chemotherapy. Patients

ABSTRACT SUMMARY Phase II Study of Bevacizumab, Cisplatin and Docetaxel Plus Maintenance Bevacizumab as First Line Treatment for Patients With Advanced Non-Small Cell Lung Cancer (n-Sq NSCLC) Combined With Exploratory Analysis of Circulating Cells (CEC): Thoracic Oncology Research Group (TORG) 1016

A phase 2 study was conducted to examine treatment with bevacizumab, cisplatin, and docetaxel followed by maintenance bevacizumab in patients with untreated, nonsquamous NSCLC (Abstract MO06.10). Eligible patients had advanced or recurrent, nonsquamous NSCLC that had not been treated with chemotherapy. Patients received 4 cycles of docetaxel (60 mg/m^2), cisplatin (80 mg/m^2), and bevacizumab (15 mg/kg) on day 1 every 3 weeks followed by bevacizumab alone as maintenance every 3 weeks until disease progression or unacceptable toxicity. The primary endpoint was ORR. Most of the 47 patients were male (60%), and their median age was 61 years (range, 39-73 years). Seventy percent were current or former smokers, and all had an ECOG PS of 0 or 1. EGFR was mutated in 28%, wild-type in 66%, and unknown in 6%. Eighty-seven percent of patients received bevacizumab maintenance. The ORR as assessed by an independent panel was 74.5%. An additional 11 patients exhibited stable disease, for a disease control rate of 97.9%. The median PFS was 9.0 months (95% CI, 7.0-11.3 months). The most common grade 3/4 AEs were neutropenia (95%), leukopenia (59%), and hypertension (47%). One patient experienced grade 5 alveolar hemorrhage after treatment cycle 4. Exploratory analysis of circulating endothelial cells at baseline and day 8 showed a superior PFS in patients whose level of circulating endothelial cells increased more than 10 counts compared with less than 10 counts (P=.033).

in arm D received high-dose radiation and chemotherapy with cetuximab, followed by chemotherapy plus cetuximab as consolidation therapy.

Enrolled patients had newly diagnosed, stage IIIA or IIIB unresectable NSCLC. Patients with supraclavicular or contralateral hilar node involvement were not eligible. Adequate PS, pulmonary function, and organ function were required. The trial opened in November 2007 and accrued a total of 544 patients. After the initial 79 patients were randomized to high-dose or standard-dose radiation, the study was amended, and patients were randomized in a 2-by-2 factorial design, with radiation dose as one factor and the addition of cetuximab as another factor. The statistical hypothesis was that each factor would increase the median OS from 17.1 months in the control arm to 24 months in the experimental arm. A 1-sided log-rank test was used, and 3 interim analyses were performed at 85, 170, and 255 events.

Dr Gregory Masters presented final results of the trial for patients who received cetuximab (n=237) vs those who did not (n=228). The study population was predominantly male (59.6%) and white (85.2%), and all patients had a Zubrod PS of 0 or 1. The majority of patients (55.7%) had nonsquamous histology and stage IIIA disease (63.9%). With a median follow-up of 18.7 months, grade 3 to 5 nonhematologic toxicities were significantly worse for patients who received cetuximab vs those who did not (70.5% vs 50.7%; $P<.0001$). Overall, grade 3 to 5 toxicities were also worse in patients randomized to cetuximab (85.2% vs 69.2%; $P<.0001$). Median OS was 23.1 months in patients who received cetuximab vs 23.5 months for chemoradiotherapy alone, with no significant difference between the 2 groups (hazard ratio [HR], 0.99; $P=.4838$; Figure 1). Median rates of progression-free survival (PFS) were also similar (10.4 months with cetuximab vs 10.7 months without [HR, 0.96; $P=.3471$]). EGFR expression in tumors was examined using the hybrid score, which is based on the intensity of EGFR staining by immunohistochemistry. Using a multivariate Cox model, tumors were equally stratified based on treatment assignment and pretreatment characteristics, except for a small imbalance in terms of histology and radiation technique. Patients with tumors showing a high hybrid score were significantly more likely to benefit from the addition of cetuximab than patients with a low hybrid score ($P=.02$).

In conclusion, cetuximab added to chemoradiotherapy did not improve OS or PFS in this population of stage III NSCLC patients. The antibody did, however, significantly increase grade 3 to 5 toxicities as compared with chemoradiation alone. High EGFR expression may help identify patients who are more likely to benefit from the addition of cetuximab to chemoradiotherapy, and further study of this effect may be warranted in patients whose tumors have high EGFR expression. As presented by Dr Bradley at the 2013 meeting of the American Society of Clinical Oncology, RTOG 0617 data showed that high-dose radiation was not superior to standard-dose radiation in this group of patients with unresectable stage 3 NSCLC.[4] Patients receiving higher-dose radiation had an increased risk of death and an increased risk of local failure. Toxicities, especially esophagitis, were also increased in the high-dose radiation group.

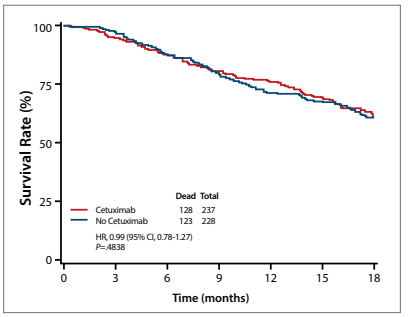

Figure 1. The addition of cetuximab to chemoradiotherapy did not improve overall survival in patients with stage III non–small cell lung cancer (NSCLC). HR, hazard ratio. Adapted from Bradley J et al. IASLC abstract PL03.05. *J Thorac Oncol*. 2013;8(suppl 2):S3.[3]

ABSTRACT SUMMARY A Phase II Trial of Paclitaxel, Pemetrexed and Bevacizumab in Patients With Untreated, Advanced Lung Cancers

Standard first-line therapy for patients with advanced NSCLC consists of a platinum doublet plus bevacizumab. However, many patients are ineligible for platinum-based therapy owing to comorbidities, such as neuropathy and renal insufficiency. To address the need for alternative regimens, a phase 2 study investigated pemetrexed, paclitaxel, and bevacizumab as first-line treatment for patients with advanced, untreated, nonsquamous NSCLC (Abstract MO06.11). Treatment consisted of pemetrexed (500 mg/m^2) on days 1 and 15; paclitaxel (90 mg/m^2) on days 1, 8, and 15; and bevacizumab (10 mg/kg) on days 1 and 15 for 6 cycles of 28 days. Maintenance therapy consisted of pemetrexed plus bevacizumab every 28 days until disease progression or unacceptable toxicity. Computed tomography scans were performed after cycles 1 and 2 and every 2 cycles thereafter. Forty-four patients were enrolled, and their median age was 59 years (range, 31-77 years). Fifty percent were male. The primary endpoint of ORR was 52% (95% CI, 37%-68%), based on 42 evaluable patients. Median PFS was 8 months (95% CI, 5.7-12.3 months), and median OS was 17 months (95% CI, 12.3-32.9 months), with 1-year OS of 64%. Meaningful responses were observed in 9 of 15 patients with *KRAS* mutations. No unexpected toxicities were observed. The most common AEs of any grade were fatigue (93%), epistaxis (87%), and alopecia (84%). The most common grade 3/4 AEs were fatigue (16%), elevated ALT (16%), and leukopenia (9%).

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MO06.12 Efficacy and Safety of Paclitaxel and Carboplatin With Bevacizumab for the First-Line Treatment of Patients With Nonsquamous Non-Small Cell Lung Cancer (NSCLC): Analyses Based on Age in the Phase 3 PointBreak and E4599 Trials

Dr Corey Langer presented a post hoc analysis of the phase 3 Eastern Cooperative Oncology Group (ECOG) 4599 and PointBreak (A Study of Pemetrexed, Carboplatin and Bevacizumab in Patients With Nonsquamous Non-Small Cell Lung Cancer) trials, which investigated the role of bevacizumab in previously untreated, nonsquamous cell, advanced NSCLC.[1-3] The trial showed that patients ages 70 years or older with advanced disease who were treated with the experimental treatment of bevacizumab added to paclitaxel plus carboplatin experienced no obvious survival benefit compared with patients younger than 70 years who received the same treatment or compared with patients of the same age treated with chemotherapy alone. In addition, a significantly increased incidence of grade 3 to 5 adverse events (AEs) was observed in the 224 patients ages 70 years or older in the bevacizumab-containing arm (87% vs 61%; *P*>.001).

To gain greater insight into the potential relationship between patient age and bevacizumab safety and efficacy in patients with advanced NSCLC, the authors analyzed data pooled from ECOG 4599 and the PointBreak trial on patients who received bevacizumab plus chemotherapy in both trials vs patients who received chemotherapy alone in ECOG 4599. Both trials enrolled treatment-naive patients with stage IIIB or IV nonsquamous cell NSCLC and an ECOG PS of 0 or 1. PointBreak included patients with stable metastases, whereas these patients were excluded from ECOG 4599. Patients received paclitaxel (200 mg/m^2), carboplatin (AUC, 6), and bevacizumab (15 mg/kg) every 3 weeks for 4

ABSTRACT SUMMARY nab-Paclitaxel Plus Carboplatin in Patients (pts) With Squamous Cell (SCC) Non-Small Cell Lung Cancer (NSCLC): Analysis of Pts Treated Beyond 4 Cycles in a Pivotal Phase 3 Trial

A pivotal phase 3 study (CA031) compared carboplatin plus either nanoparticle albumin-bound (*nab*)-paclitaxel or soluble (sb)-paclitaxel in untreated, stage IIIB or IV NSCLC (Socinski MA et al. *Ann Oncol*. 2013;24(9):2390-2396). In the subset of patients with squamous cell carcinoma, *nab*-paclitaxel yielded a 68% improvement in ORR and showed a trend toward improved survival (median OS, 10.7 months vs 9.5 months; *P*=.808). Data were presented from an analysis of the 229 patients with squamous cell carcinoma who received maintenance therapy after their initial induction treatment (Abstract MO24.07).[2] Patients received 4 cycles of induction therapy consisting of *nab*-paclitaxel (100 mg/m^2) every week plus carboplatin (AUC, 6) every 3 weeks. The 138 (60%) patients who were progression-free after cycle 4 then entered into cycle 5 and were the subject of the current analysis. These patients had a median age of 58 years. Most patients were male (91%), and all had an ECOG PS of 0 (21%) or 1. Eighty-two percent of patients were current or former smokers. As measured from day 1 of treatment cycle 5, median PFS was 3.4 months (range, 2.8-4.2 months), and median OS was 10.3 months (range, 8.9-14.1 months). As measured from day 1 of treatment cycle 1, median PFS was 6.8 months (range, 5.7-7.2 months), and median OS was 13.8 months (range, 12.4-16.8 months). *nab*-Paclitaxel was generally well tolerated, with safety outcomes similar to those observed in the entire CA031 study population. The most common AEs of grade 3 or higher were neutropenia (49%), anemia (31%), and thrombocytopenia (27%). Sensory neuropathy was uncommon: 5 patients (4%) experienced grade 3 sensory neuropathy, and no grade 4 incidents were reported. Grade 3 peripheral neuropathy occurred at cycles 6, 8, and 10, in 1%, 3%, and 0% of patients, respectively.

cycles (PointBreak) or 6 cycles (ECOG 4599) followed by maintenance bevacizumab until disease progression or unacceptable toxicity. Patient-level data were pooled. Patients were stratified by age: younger than 65 years, 65 to 74 years, 70 to 75 years, younger than 75 years, and 75 years or older. In PointBreak, analyses by age using a cutoff of 70 years were prespecified.

PFS and OS were assessed by Kaplan-Meier analysis. Outcomes in patients who received bevacizumab were compared with those from patients who received paclitaxel and carboplatin alone in ECOG 4599, using a Cox proportional hazard model that adjusted for imbalances in patient baseline characteristics. The comparison demonstrated a PFS benefit for every age group, including patients younger than 75 years, with HRs ranging from 0.57 to 0.71. However, for patients ages 75 years or older, there was no benefit (95% CI, 0.62-1.44; HR, 0.95). Similarly, an OS benefit was observed in the same age groups, with HRs ranging from 0.68 to 0.80. In patients 75 years or older, however, the HR was 1.05 (95% CI, 0.70-1.57).

Among patients younger than 75 years, Kaplan-Meier analysis showed a median OS of 13.4 months for those treated with bevacizumab and chemotherapy vs 10.2 months for those who received chemotherapy alone (HR, 0.78; 95% CI, 0.68-0.89; *P*<.001; Figure 2). In contrast, among patients ages 75 years or older, median OS was 9.6 months among those who received bevacizumab vs 13.0 months in those who did not (95% CI, 0.70-1.57; HR, 1.05). Although patients younger than 75 years experienced a greater incidence of grade 3 to 5 AEs with bevacizumab (63%) vs chemotherapy alone (48%; *P*<.005), patients ages 75 years or older experienced an elevated incidence of grade 3 to 5 AEs in both arms, with a marked increase in the bevacizumab arm (81% with bevacizumab vs 56% without; *P*<.005). Moreover, grade 5 toxicities were increased 4-fold with the inclusion of bevacizumab among patients 75 years or older (8% vs 2%). Patients who received bevacizumab also had higher rates of treatment discontinuation, which were exacerbated in patients 75 years or older (29% vs 19%) compared with patients younger than 75 years (17% vs 12%).

The speaker concluded that the data pointed to a clinically meaningful OS and PFS benefit with the addition of bevacizumab to paclitaxel and carboplatin for patients younger than 75 years, but not for patients 75 years or older. The high incidence of grade 5 events in patients 75 years or older treated with bevacizumab highlights the need for caution when administering bevacizumab to these patients, although firm conclusions cannot be drawn from this analysis owing to the relatively limited number of patients.

ABSTRACT SUMMARY Addition of Bevacizumab (BEV) to Pemetrexed (PEM) Plus Cisplatin (CIS) Induction and PEM Maintenance Therapy in 1st Line Setting for Treatment of Advanced Nonsquamous Non Small Cell Lung Cancer (NS-NSCLC)—Final Results and Safety Update From a Phase 2 Study

A phase 2 study examined the efficacy and safety of first-line pemetrexed, cisplatin, and bevacizumab induction therapy followed by pemetrexed plus bevacizumab in patients with advanced NSCLC (Abstract P2.10-004). Enrolled patients had nonsquamous, stage IIIB or IV NSCLC and an ECOG PS of 0 or 1. Induction treatment included 4 cycles of pemetrexed (500 mg/m^2), cisplatin (75 mg/m^2), and bevacizumab (7.5 mg/kg) on day 1 of each 3-week cycle followed by pemetrexed plus bevacizumab as maintenance treatment. The 109 enrolled patients were a median age of 60.6 years (range, 38.4-76.9 years), 58.7% of patients were male, 86.3% were current or former smokers, and 90.8% of patients had stage IV disease. The primary endpoint of median PFS was 6.9 months (90% CI, 5.7-8.3 months) for the overall study population and 9.1 months (90% CI, 7.3-11.4 months) for the 72 patients in the maintenance population. Median OS was 14.7 months (95% CI, 11.5-19.7 months) for all study patients vs 19.7 months (95% CI, 14.9-25.9 months) for patients who received maintenance treatment. ORR was 42.2%, with no complete responses. No unexpected toxicities were observed. The most common grade 3/4 AEs of any grade were nausea (61.5%), fatigue (55.1%), and constipation (36.7%). Grade 3/4 AEs that were possibly related to treatment with bevacizumab included hypertension (5.5%), thromboembolic events (2.7%), and gastrointestinal complications (1.8%). Two patients died from toxicity related to the study drug, including 1 case each of gastrointestinal hemorrhage and aspiration pneumonia.

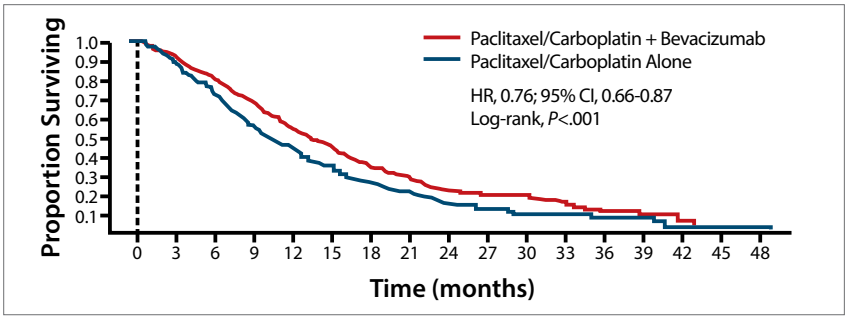

Figure 2. Bevacizumab improved overall survival when added to chemotherapy in patients with previously untreated, nonsquamous cell, advanced non–small cell lung cancer who were younger than 75 years. HR, hazard ratio. Adapted from Langer CJ et al. IASLC abstract MO06.12. *J Thorac Oncol.* 2013;8(suppl 2):S291.[3]

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O02.03 Value of Adding Erlotinib to Thoracic Radiation Therapy With Chemotherapy for Stage III Non-Small Cell Lung Cancer: A Prospective Phase II Study

Dr Ristuko Komaki presented data from a phase 2 trial that tested erlotinib as a radiosensitizer in conjunction with thoracic radiation among patients with previously untreated, locally advanced, inoperable NSCLC.[1] The trial enrolled 48 patients with a Karnofsky performance score of greater than 70, weight loss of at least 5% throughout the previous 3 months, and adequate organ function. The primary endpoint was time to progression. Patients had a median age of 63 years (range, 46-81 years), 63% were male, and 87% were current or former smokers. Half of the patients had adenocarcinoma.

Patients were treated for a total of 7 weekly cycles. On days 1 to 5 of each week, patients received radiation at a dosage of 1.8 Gy daily, for a total of 63 Gy. On day 1, patients received carboplatin (AUC, 2) and paclitaxel (45 mg/m^2). On days 2 to 7, patients received erlotinib (150 mg/m^2). Therefore, patients received concurrent chemotherapy and radiation on day 1, concurrent erlotinib and radiation on days 2 to 5, and erlotinib alone on days 6 to 7. Patients received no treatment during weeks 8 to 11, followed by consolidation chemotherapy consisting of 2 cycles of carboplatin (AUC 6) and paclitaxel (200 mg/m^2) during weeks 12 to 17. EGFR mutation analysis was performed on tumors from 41 patients. Responses were evaluated by computed tomography scans taken after completion of consolidation chemotherapy.

Table 1. Outcome of a Prospective Phase 2 Study of Erlotinib, Thoracic Radiation, and Chemotherapy in Stage III NSCLC

	Overall Survival	Progression-Free Survival	Local Relapse-Free Survival	Distant Metastasis-Free Survival
Median Survival (months)	34.1	13.7	Not reached	18.2
12 Months	82.9%	55.7%	74.6%	66.3%
24 Months	67.7%	31.8%	59.7%	44.3%
36 Months	48.3%	24.5%	59.7%	32.2%

NSCLC, non–small cell lung cancer.

Data from Komaki R et al. IASLC abstract O02.03. *J Thorac Oncol*. 2013;8(suppl 2).[1]

Available data from 46 patients showed 30% complete responses and 50% partial responses. Three (75%) of the 4 patients with mutant EGFR experienced a complete response vs 11 (30%) of 36 patients with wild-type EGFR. Median OS was 34.1 months, median PFS was 13.7 months, and 2-year OS was 68% (Table 1). Comparing data from the current trial with historic data from 66 patients treated with a combination of carboplatin, docetaxel, and concurrent radiation suggested that erlotinib improved OS in this patient population (P=.0098). Reported toxicities included 1 (2%) case of esophagitis, 2 (4%) cases of acne, and 3 (7%) cases of pneumonitis, all grade 3. No grade 4 or 5 AEs occurred.

Reference

1. Komaki R, Allen PK, Wei X, et al. Value of adding erlotinib to thoracic radiation therapy with chemotherapy for stage III non-small cell lung cancer: a prospective phase II study. [IASLC abstract O02.03]. *J Thorac Oncol*. 2013;8(suppl 2).

AVASTIN® (bevacizumab)

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.

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 5, 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.

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03/13 AVA0000764705
Initial U.S. Approval: February 2004
Code Revision Date: March 2013

ABSTRACT SUMMARY Efficacy and Safety of Erlotinib in Elderly Vs Non-Elderly Patients: Analysis of the POLARSTAR Study of 9,909 Japanese Non-Small Cell Lung Cancer (NSCLC) Patients Treated With Erlotinib

Elderly NSCLC patients often present with comorbidities that can limit treatments. Erlotinib has demonstrated improved survival with good tolerability, particularly in comparison with cytotoxic agents, in previously treated NSCLC. The POLARSTAR (Postmarketing Surveillance Study of Erlotinib in Japanese Patients With Non–Small-Cell Lung Cancer [NSCLC]) surveillance study was conducted to investigate erlotinib safety and efficacy, with a primary endpoint of the occurrence of interstitial lung disease and risk factors for its onset (Nakagawa et al. *J Thorac Oncol*. 2012;7(8):1296-1303). This Japanese study enrolled patients with unresectable, recurrent, and/or advanced NSCLC treated with erlotinib from December 2007 through October 2009. Dr Taro Koba presented an exploratory analysis of erlotinib efficacy and safety data by age group, ECOG PS, and prior gefitinib therapy (Abstract P2.10-028). The safety analysis included a total of 9907 patients divided into 3 groups: A (<75 years; n=7848 [79.2%]), B (75-84 years; n=1911 [19.3%]), and C (≥85 years; n=148 [1.5%]). The efficacy analysis included 9651 patients divided into similar groups: A (<75 years, n=7701 [79.8%]), B (75-84 years; n=1815 [18.8%]), and C (≥85 years; n=135 [1.4%]). Fifty-three percent of patients were male, and 26.0% had an ECOG PS of 2 or greater. Most patients (80.2%) had adenocarcinoma, 49.6% had stage IV disease, and one-third had brain metastases. Nearly 45% of patients had previously received gefitinib. Baseline characteristics were well balanced among the groups. No new toxicity issues were raised, and tolerability was acceptable not only for younger patients, as previously reported, but also for patients 75 years or older. Grade 5 nonhematologic toxicities were reported in 2.0% of patients in group A, 2.3% of patients in group B, and 2.7% of patients in group C. One patient in group A had grade 5 anemia, and 1 patient in group B had grade 5 thrombocytopenia. PFS did not differ according to age (group A: 65 days; group B: 74 days; group C: 72 days). In patients with clinical features associated with better *EGFR* TKI efficacy—including adenocarcinoma, nonsmoker, ECOG PS of 0 to 2, and second- or third-line treatment setting—the median PFS was not numerically inferior for patients in group B or C compared with those in group A among patients who had received prior gefitinib as well as those who had not. Median PFS was also not numerically inferior for patients in group B or C compared with patients in group A when analyzed by ECOG PS of 0 to 2 vs 3 to 4. The authors concluded that erlotinib could be considered standard therapy for elderly NSCLC patients in second-line or later treatment settings.

MO06.03 Bevacizumab and Erlotinib or Bevacizumab, Cisplatin and Pemetrexed in Patients With Metastatic Non-Small Cell Lung Cancer: EGFR Mutation Based Treatment Allocation and Repeat Biopsy at Progression in the SAKK19/09 (BIOPRO) Trial

Dr Oliver Gautschi presented results from a multicenter, nonrandomized, phase 2 trial (Swiss Group for Clinical Research [SAKK] study 19/09; NCT01116219), which prospectively tested pemetrexed and bevacizumab maintenance therapy in patients with metastatic, nonsquamous cell NSCLC with wild-type EGFR.[1] The study's design was prompted by several recent findings. Treatment allocation based on EGFR mutation status and the inclusion of maintenance therapy is the new standard. Maintenance therapy with pemetrexed and bevacizumab is a new option based on findings from the PointBreak trial.[2] Additionally, results from SAKK19/05 suggested that the combination of erlotinib plus bevacizumab was promising.[3] In SAKK19/09, patients had to consent to repeat biopsy at progression to enable the study of molecular mechanisms of drug resistance. Patients with wild-type EGFR received 4 cycles of cisplatin (75 mg/m^2), pemetrexed (500 mg/m^2), and bevacizumab (7.5 mg/kg) every 3 weeks followed by maintenance therapy with pemetrexed and bevacizumab until progression. Patients with mutated EGFR received bevacizumab (7.5 mg/kg) every 3 weeks and erlotinib (150 mg) daily until progression. The primary endpoint was PFS at 6 months. Secondary endpoints included further biomarker analysis.

Seventy-seven patients with wild-type EGFR and 20 patients with mutated EGFR were evaluable. No unexpected toxicities were observed. Among patients with wild-type EGFR, PFS at 6 months was 45.5% (95% CI, 34.1%-57.2%), which met the primary endpoint. Median PFS was 6.9 months (95% CI, 4.6-8.3 months; Figure 3), and median OS was 12.1 months (95% CI, 8.7-14.7 months). ORR was 62%, and 16 patients (21%) remained on treatment. KRAS mutation, observed in 30% of patients with wild-type EGFR, was associated with poor OS (95% CI, 1.05-3.88; HR, 2.0; *P*=.03), but not with PFS or best response outcomes. For patients with a mutated EGFR, PFS at 6 months was 70.0% (95% CI, 45.7%-88.1%), median PFS was 14.0 months (95% CI, 8.8 months-not reached), and median OS was not reached. The ORR was 70%, and 11 patients (55%) remained on treatment. Although the PointBreak trial administered bevacizumab, cisplatin, and pemetrexed to patients who were not screened for EGFR status, the current trial used the same therapy and yielded similar survival rates in patients selected for wild-type EGFR. First-line erlotinib plus bevacizumab is being investigated in the BELIEF (Bevacizumab and Erlotinib in EGFR Mut+ NSCLC) trial.[4]

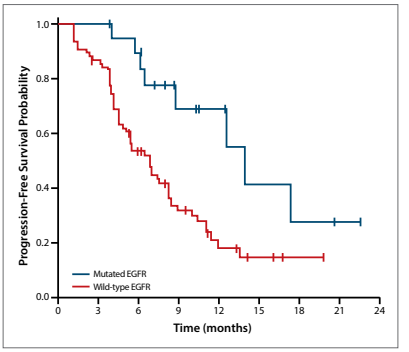

Figure 3. Progression-free survival in a study that based treatment on *EGFR* mutations. Patients with wild-type *EGFR* received 4 cycles of cisplatin, pemetrexed, and bevacizumab every 3 weeks followed by maintenance therapy with pemetrexed and bevacizumab until progression. Patients with mutated *EGFR* received bevacizumab every 3 weeks and erlotinib daily until progression. *EGFR*, epidermal growth factor receptor. Adapted from Gautschi O et al. IASLC abstract MO06.03. *J Thorac Oncol*. 2013;8(suppl 2):S287.[1]

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Clinical Trials of PD-1 and PD-L1 Inhibitors in NSCLC

An important mechanism that promotes tumor survival is the ability of tumor cells to evade attack by the immune system.[1] Tumor-infiltrating lymphocytes lose their effectiveness owing to the immunosuppressive environment of the tumor, as well as their expression of programmed death 1 (PD-1), a receptor that inhibits T-cell activity and is frequently expressed on tumor-infiltrating lymphocytes. The ligands PD-L1 and PD-L2 are expressed in some tumor types, including a subset of lung cancer tumors, and inhibit the effector functions of cytotoxic T cells. By disrupting this inhibitory pathway, antibodies that block the interaction between PD-1 and its ligands may restore antitumoral immunologic activity.

The novel agent MPDL3280A is an antibody against PD-L1. In a phase 1 dose escalation and expansion study, patients with metastatic, solid tumors were treated with MPDL3280A once every 3 weeks for up to 16 cycles or approximately 1 year.[2] Results of the trial were presented by Dr Leora Horn. The primary endpoints were safety and tolerability, and responses were assessed based on Response Evaluation Criteria In Solid Tumors (RECIST) 1.1.[3] The 85 enrolled NSCLC patients had a median age of 60 years (range, 24-84 years), and 56% were male. All patients had an ECOG PS of 0 (32%) or 1 (68%). Seventy-six percent of patients had tumors with nonsquamous cell histology; 55% had received at least 3 prior systemic regimens, and 80% were current or former smokers.

Most AEs were grade 1 or 2 and did not require intervention. The most common AEs of any grade were fatigue (20%), nausea (14%), and anorexia (12%). There were very few grade 3 or 4 AEs; no grade 3 to 5 pneumonitis was observed, and no DLTs were observed with antibody doses up to 20 mg/kg. Immune-related, grade 3/4 AEs were observed in 1 patient with large-cell neuroendocrine NSCLC who developed diabetes mellitus. There was 1 treatment-related death. The ORR was 23% (Figure 4). Tumors from 6 patients yielded an immunohistochemistry (IHC) score of 3 for detection of PD-L1, and these patients had an ORR of 83%. The combined group of 13 patients with IHC scores of 2 or 3 had an ORR of 46%, and the group of 26 patients with an IHC score of 1, 2, or 3 had an ORR of 31% (8 of 26 patients), consistent with the antibody's proposed mechanism of action. Patients who responded to treatment included those with squamous and nonsquamous cell histology. Responses were both rapid and durable, with the majority of patients having completed treatment at the time of the presentation and without requiring re-treatment on study. Current and former smokers (n=43) demonstrated a higher ORR compared with patients who had never smoked (n=10; 26% vs 10%). A slightly improved response was seen in patients with wild-type (n=40) vs mutant EGFR (n=6; 23% vs 17%), and a more robust difference was observed in patients with wild-type (n=27) vs mutant KRAS (n=10; 30% vs 10%).

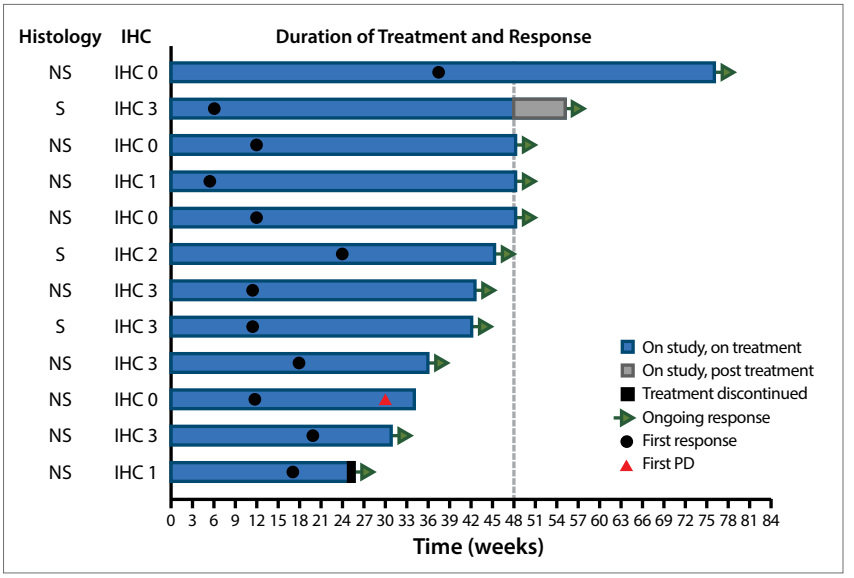

Figure 4. Best response to MPDL3280A, an antibody against PD-L1, according to smoking histology and immunohistochemistry status in patients with non–small cell lung cancer. IHC, immunohistochemistry; NS, nonsmoker; PD, progressive disease; S, smoker. Data from Horn L et al. IASLC abstract MO18.01. *J Thorac Oncol.* 2013;8(suppl 2):S364.[2]

Dr Edward Garon presented preliminary safety and efficacy data from a phase 1 trial investigating MK-3475, a humanized IgG4 antibody that binds to PD-1 with high affinity and has demonstrated activity in melanoma.[4,5] Because the antibody does not induce antibody-directed cellular toxicity, it binds to the PD-1 receptor without inducing T-cell death. The objectives of part C of this phase 1 protocol were to assess safety and efficacy in previously treated NSCLC. Eligibility requirements included measurable disease, an ECOG PS of 0 or 1, and 2 prior systemic therapies. All patients were required to submit a new tumor specimen so that expression levels of PD-L1 could be assessed. MK-3475 was administered at 10 mg/kg intravenously every 3 weeks.

Table 2. Preliminary Data From a Phase 1 Trial of MK-3475 in Previously Treated NSCLC

	Immune-Related Response Criteria, Investigator Review			RECIST v1.1, Independent Review			Median OS, Weeks (95% CI)
Subgroup	N	ORR, n (%) (95% CI)	Median PFS, weeks (95% CI)	N	ORR* (%) (95% CI)	Median PFS, weeks (95% CI)	
All	38	9 (24%) (11%- 40%)	9.1 (8.3-17.4)	33	7 (21%) (9%-39%)	9.7 (7.6-17)	51 (14-NR)
Nonsquamous	31	7 (23%) (10%-41%)	9.1 (8.3-17.0)	26	4 (16%) (4%-35%)	10.3 (7.6-17)	35 (14-NR)
Squamous	6	2 (33%) (4%-78%)	23.5 (2.7–NR)	6	2 (33%) (4%-78%)	15.2 (1.4-NR)	NR (2.7-NR)

*Response rate per RECIST V1.1 is based on patients with at least 1 measurable lesion at baseline per central review. All but 2 responses were confirmed.

NR, not reached; ORR, overall response rate; OS, overall survival; NSCLC, non–small cell lung cancer; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors.

Data from Garon EB et al. Preliminary clinical safety and activity of MK-3475 monotherapy for the treatment of previously treated patients with non-small cell lung cancer (NSCLC) [IASLC abstract MO18.02]. *J Thorac Oncol. 2013;8(suppl 2):S364.*[4]

Of the 38 enrolled patients, 42% were male, 45% were 65 years or older, and 58% had an ECOG PS of 1. Sixty-six percent were current or former smokers, 16% had tumors with squamous cell histology, and 11% had brain metastases that had been treated. PD-L1 expression was observed in 61% of tumors, 26% were negative, and 13% were not evaluable. The potential cut point was determined by the Youden Index from a receiver operator characteristics curve.

Approximately half of patients (53%) experienced at least 1 drug-related AE of any grade. The most common drug-related AEs, occurring in at least 10% of patients, were rash (21%), pruritus (18%), fatigue (16%), diarrhea (13%), and arthralgia (11%). Other AEs considered drug-related were 1 case each of hyperthyroidism, hypothyroidism, and pneumonitis, all grade 2, and 1 occurrence of grade 3 pulmonary edema. The ORR was 24% (95% CI, 11%-40%) based on investigator assessment following immune-related response criteria and 21% (95% CI, 9%-39%) based on independent review using RECIST 1.1 (Table 2).[3,6] Median PFS was 9.1 weeks (95% CI, 8.3-17.4 weeks) by investigator review and 9.7 weeks (95% CI, 7.6-17 weeks) by independent review. The median OS for the entire cohort was 51 weeks (95% CI, 14 weeks-not reached). At a median follow-up of 9 months, 2 patients had progressed. At the time of data analysis, 7 of the 9 patients with a response remained on treatment, and median PFS for these patients had not been reached.

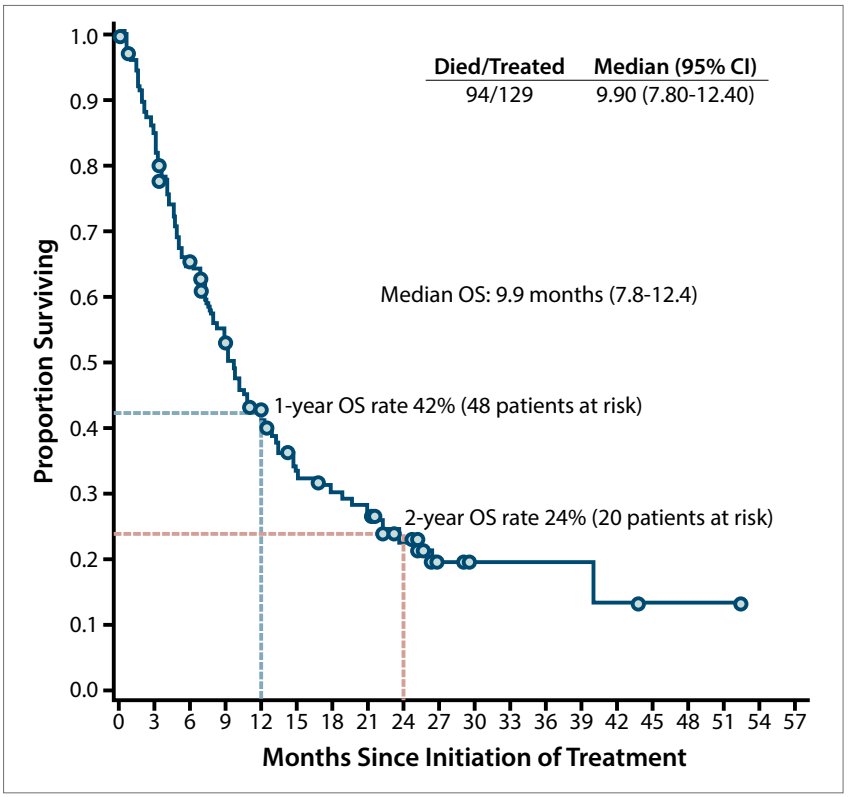

Figure 5. Updated overall survival (OS) from a phase 1 trial of nivolumab, a fully human IgG4 antibody against PD-1, in patients with non–small cell lung cancer. Adapted from Brahmer JR et al. IASLC abstract MO18.03. *J Thorac Oncol.* 2013;8(suppl 2):S365.[7]

Dr Julie Brahmer presented updated OS and long-term safety data from a phase 1 trial of nivolumab, a fully human immunoglobulin G4 antibody against PD-1.[7] The trial enrolled 129 NSCLC patients. The patients' median age was 65 years, and 99% of patients had an ECOG PS of 0 or 1. Fifty-seven percent had non-

ABSTRACT SUMMARY BEYOND: A Randomized, Double-Blind, Placebo-Controlled, Multicentre, Phase III Study of First-Line Carboplatin/Paclitaxel (CP) Plus Bevacizumab (Bv) or Placebo (Pl) in Chinese Patients With Advanced or Recurrent Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Pivotal studies that demonstrated the benefit of adding bevacizumab to a platinum doublet as first-line treatment for nonsquamous NSCLC were performed mostly in white patients. (Sandler A et al. *N Engl J Med*. 2006;355(24):2542-2550; Reck M et al. *J Clin Oncol*. 2009;27(8):1227-1234). Subgroup analyses suggested a benefit in Asian patients. The phase 3 BEYOND (A Randomized, Double-Blind, Placebo-Controlled, Multicentre, Phase III Study of First-Line Carboplatin/Paclitaxel [CP] Plus Bevacizumab [Bv] or Placebo [Pl] in Chinese Patients With Advanced or Recurrent Non-Squamous Non-Small Cell Lung Cancer [NSCLC]) study was undertaken to evaluate the safety and efficacy of this drug combination in a Chinese patient population. Enrolled patients had untreated, advanced or metastatic, nonsquamous NSCLC and an ECOG PS of 0 to 1. After stratification by sex, smoking status, and age, the study randomized 276 patients to receive paclitaxel (175 mg/m^2) and carboplatin (AUC, 6) plus either bevacizumab (15 mg/kg) or placebo on day 1 of each 3-week cycle for up to 6 cycles, followed by maintenance bevacizumab or placebo. The primary endpoint was PFS. Blood samples were collected for biomarker analyses at baseline, every 2 cycles during treatment, at progression, and at 4 to 6 weeks after progression. Tissue sample collection was optional. Median PFS was superior in patients who received bevacizumab (9.2 months vs 6.5 months; 95% CI, 0.29-0.54; HR, 0.40; *P*<.0001). The addition of bevacizumab also improved ORR (54.4% vs 26.3%; *P*<.0001) and median duration of response (8.0 months vs 5.3 months). OS data were not mature at the time of the presentation. Baseline plasma levels of vascular endothelial growth factor A and vascular endothelial growth factor receptor 2 did not correlate with bevacizumab efficacy. Tolerability was similar for both regimens, and no new safety signals were observed. AEs of grade 3 or higher occurred in 67.0% of patients who received bevacizumab vs 61.0% of patients in the control arm. Thirteen percent of patients in each arm experienced serious AEs, and treatment-related deaths occurred in 2.2% of patients who received bevacizumab vs 0.8% of patients in the control arm.

squamous cell histology, and 42% had squamous cell histology. One patient's tumor histology was unknown. Fifty-four percent of patients had received at least 3 prior therapies. Patients were randomized to receive nivolumab intravenously every 2 weeks for a maximum of 12 eight-week cycles at doses of 1 mg/kg (n=33), 3 mg/kg (n=37), or 10 mg/kg (n=59). In the 3 arms combined, ORR was 17.1%, and the median duration of response was 74 weeks (range, 6.1-133.9 weeks). A dose response was observed at the 3 levels tested, with ORRs of 3.0%, 24.3%, and 20.3% for patients who received doses of 1 mg/kg, 3 mg/kg, and 10 mg/kg, respectively. Responses were durable and ongoing in 45% of patients, and responses continued in some patients who had stopped therapy for reasons other than disease progression and had been off-treatment for at least 1 year. At the time of the first assessment, after 8 weeks of treatment, more than 50% of patients showed evidence of a response. One- and 2-year OS rates were 42% and 24%, respectively, and median OS was 9.9 months (95% CI, 7.8-12.4 months; Figure 5).

Nivolumab was generally well tolerated. Safety data were presented for treatment-related AEs with potential immunologic etiologies that might require special monitoring and/or intervention. The most common of these AEs were skin (20%), gastrointestinal (15%), and pulmonary (9%) toxicities. Grade 3/4 treatment-related AEs with potential immunologic etiologies included gastrointestinal (1%), pulmonary (2%), and hepatic (1%) events, as well as infusion reactions (1%). Six percent of patients experienced drug-related pneumonitis of any grade. Among 3 patients who experienced grade 3/4 pneumonitis, 2 died. Nivolumab is being investigated in phase 3 trials in patients with NSCLC.

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Commentary: Highlights in NSCLC From the 15th World Conference on Lung Cancer

Heather A. Wakelee, MD

The 15th World Conference on Lung Cancer (WCLC), organized by the International Association for the Study of Lung Cancer, was held in Sydney, Australia in October 2013. More than 2000 abstracts were presented, and many focused on the management of patients with NSCLC.

Updates in Chemotherapy Regimens

Nab-paclitaxel is approved as a first-line agent in combination with carboplatin for advanced-stage NSCLC, but questions remain regarding its role in the maintenance setting. Dr David R. Spigel examined maintenance therapy with *nab*-paclitaxel and carboplatin[1] in an analysis of data from the pivotal phase 3 trial of this regimen.[2] This analysis focused on patients who were able to continue treatment beyond the 4 cycles that were the treatment in the primary study. Approximately 60% of the study population was able to do so. In these patients, the median overall survival was approximately 10 months counting from the beginning of cycle 5 (approximately 3 months into therapy), with a median survival of just over 1 year counting from enrollment into the trial. PFS was just over 3 months. This analysis provides support for further evaluation of the use of *nab*-paclitaxel and carboplatin in a maintenance setting, but leaves open the question of whether *nab*-paclitaxel can be used in the maintenance setting as a single agent. It is hoped that further trials to explore these issues will be reported in the future.

Data were presented from the Spanish Lung Cancer Group's customized chemotherapy trial in advanced-stage NSCLC, which unfortunately failed to show a benefit with this approach.[3] Similarly negative results were presented in the spring of 2013 by another group, which had used ERCC1 and RRM1 levels to customize chemotherapy, but did not show a survival benefit in the customized arm.[4,5] In the Spanish Lung Cancer Group trial, advanced-stage patients were randomized to receive customized chemotherapy, selected by *BRCA1* and *RAP80* status, vs a standard arm of cisplatin/docetaxel. There was no benefit in the customized chemotherapy arm, mostly due to inferior outcomes in the patients assigned to single-agent docetaxel vs a platinum doublet. Taken together, these 2 trials indicate that DNA repair enzyme levels cannot currently be used to customize chemotherapy regimens.

Bevacizumab Combinations

In the United States, one approved treatment option for patients with advanced or recurrent NSCLC is bevacizumab in combination with carboplatin and paclitaxel. Recent studies, including trials using pemetrexed instead of paclitaxel, have failed to demonstrate improved overall survival outcomes, although toxicity differences are apparent.[6] Several presentations at the WCLC provided data on the use of bevacizumab in other chemotherapy combinations. Dr Ken Katono from Japan presented results from a nonrandomized, phase 2 study of first-line treatment with bevacizumab, cisplatin, and docetaxel followed by maintenance bevacizumab.[7] This study included an interesting analysis of whether circulating endothelial cells could provide an early indication of benefit. The drugs were administered as follows: bevacizumab at 15 mg/kg, cisplatin at 80 mg/m^2, and docetaxel at 60 mg/m^2, which is the standard dose in Japan. PFS was quite good, at 9 months. Overall survival had not been reached, but it was 89% at 1 year. The response rate was 75%. Even after considering that outcomes in Japanese studies of patients with advanced-stage, non–small cell lung cancer are usually better than those for US studies, these results are striking. As this is a nonrandomized phase 2 study, however, further work will be necessary before this approach can be widely adopted.

The data on circulating endothelial cell data were also intriguing. When circulating endothelial cell numbers increased by day 8, patients did better. This finding might be hypothesis-generating; it appears to suggest that circulating endothelial cells might have potential for use as a biomarker of bevacizumab and/or chemotherapy activity.

A study from Memorial Sloan-Kettering Cancer Center examined a nonplatinum doublet of paclitaxel, pemetrexed, and bevacizumab in a nonrandomized, phase 2 trial.[8] The median PFS was 8 months, and overall survival was 17 months, with a response rate of 52%. These outcomes are as good, if not better, than many of the platinum combinations under study. It should be noted, however, that this study was nonrandomized and performed in a patient population from a single institution. This study and the one by Dr Katono[7] will not be practice-changing, but they do provide support for the use of bevacizumab in combination with other first-line doublets.

A double-blind, randomized, placebo-controlled, phase 3 trial from China[9] followed a similar design to the ECOG 4599 trial,[10] but with a placebo arm. It examined carboplatin and pacli-

ABSTRACT SUMMARY A Randomised Placebo-Controlled Multicentre Phase II Trial of Erlotinib Plus Whole Brain Radiotherapy for Patients With Advanced Non-Small Cell Lung Cancer With Multiple Brain Metastases (TACTIC)

NSCLC patients with brain metastases have a poor median survival. Based on the potential radiosensitizing properties of erlotinib, the TACTIC (WBRT and Erlotinib in Advanced NSCLC and Brain Metastases) study was conducted to evaluate concurrent erlotinib plus whole brain radiotherapy (WBRT) followed by maintenance erlotinib in patients with untreated brain metastases (Abstract MO07.11). The study enrolled 80 patients with NSCLC and newly diagnosed brain metastases with a Karnofsky performance score of at least 70. All patients received standard WBRT administered in 5 daily fractions to 20 Gy. In addition to WBRT, patients received daily erlotinib (100 mg) or placebo followed by maintenance erlotinib (150 mg) daily. Patients had a median age of 61.8 years (range, 41-75 years). Slightly more women were randomized to erlotinib (62.5%) vs placebo (47.5%). Sixty-one percent of patients had 3 or fewer brain metastases, with the remainder having more than 3. Two months after completion of WBRT, 15 patients (37.5%) from each arm were alive and without neurologic progression. Median neurologic PFS, the primary endpoint, was 1.6 months in both arms (95% CI, 0.59-1.54; HR, 0.95; *P*=.84). Median OS was 3.4 months for erlotinib and 2.9 months for placebo (95% CI, 0.58-1.55; HR, 0.95; *P*=.83). Only 1 patient with an available sample had activating *EGFR* mutations. The frequency of grade 3/4 AEs was 70% for each arm. The erlotinib arm included more patients with grade 3/4 rash (20% vs 5%), and fewer patients with grade 3/4 fatigue (17% vs 35%).

taxel with bevacizumab or placebo. (In the ECOG 4599 trial, patients were randomized to receive or not receive bevacizumab, and no placebo was offered.) In the Chinese study, the addition of bevacizumab significantly improved PFS (9.2 months vs 6.5 months; hazard ratio, 0.4). Survival outcomes were not yet available, and they will be needed before these results can be considered confirmation of those from ECOG 4599.

This study also examined the use of biomarkers, such as vascular endothelial growth factor A and vascular endothelial growth factor receptor 2, but no correlation to the efficacy of bevacizumab was found. Regardless of the *EGFR* mutation status, bevacizumab provided benefit when added to carboplatin/paclitaxel, which is an important finding given the frequency of *EGFR* mutations in the tumors of Chinese NSCLC patients.[11]

A retrospective analysis of data from the ECOG 4599 trial[10] and the PointBreak (A Study of Pemetrexed, Carboplatin and Bevacizumab in Patients With Nonsquamous Non-Small Cell Lung Cancer) trial[12] examined age and safety in patients receiving paclitaxel, carboplatin, and bevacizumab.[13] This analysis considered ECOG 4599 separately and also looked at the pooled data. For all patients younger than 75 years, there was a clear survival benefit with the bevacizumab. Among patients older than 75 years, the addition of bevacizumab did not seem to provide benefit. According to Kaplan-Meier analysis, for patients younger than 75 years, overall survival was 13.4 months with bevacizumab vs 10.2 months without (hazard ratio, 0.78), which confirms earlier findings. Among patients older than 75 years, a survival detriment of approximately 3 months was associated with the addition of bevacizumab, however, this result was not statistically significant.

A Swiss trial also explored other bevacizumab combination regimens in patients with newly diagnosed NSCLC.[14] An *EGFR* mutation was identified in approximately 20 patients, all of whom received erlotinib and bevacizumab. Patients who were wild-type for *EGFR* were randomized to receive pemetrexed and cisplatin, with or without bevacizumab, and then maintenance with pemetrexed, with or without bevacizumab. For patients with *EGFR* mutations, the overall response rate was 70%, and at 6 months, PFS was 70.0%. More data will be needed from this trial to interpret the results.

The Chinese Thoracic Oncology Group 0806 Study was a randomized phase 2 trial examining pemetrexed vs gefitinib as second-line treatment in advanced-stage *EGFR* wild-type patients previously treated with a platinum doublet.[15] Among the 157 patients, 81 received pemetrexed and 76 received gefitinib. PFS clearly favored pemetrexed, and although the difference in overall survival was not statistically significant, it also trended in favor of the pemetrexed. This study provides additional data supporting the use of chemotherapy instead of *EGFR*-targeted agents as second-line therapy in patients without an *EGFR* mutation. There is probably still a role for *EGFR*-targeted therapy in some *EGFR* wild-type patients, but more exploratory efforts will be needed to identify patients who will benefit from these drugs.

The Addition of EGFR-Targeted Agents to Radiation

In the plenary session, Dr Gregory A. Masters presented results from the Radiation Therapy Oncology Group (RTOG) Study 0617.[16] This study examined standard-dose vs high-dose radiation with or without cetuximab. An earlier analysis of this study, presented at the 2013 ASCO meeting, showed that high-dose radiation at 74 Gy was inferior to the standard dose radiation of 60 Gy.[17] Dr Master's presentation at the WCLC included

the data on cetuximab. In this 4-arm study, all patients received standard chemotherapy with carboplatin and paclitaxel. Patients were randomized to receive 1 of 2 radiation regimens: 60 Gy 5 times a week for 6 weeks or 74 Gy 5 times a week for 7.5 weeks. Both of these radiation regimens were administered with or without cetuximab. Consolidation therapy consisted of chemotherapy in all patients, with the addition of cetuximab in those patients who received it initially.

There was no benefit in overall survival for the patients who received cetuximab (hazard ratio, 0.99). Analyses of *EGFR* protein expression by IHC were performed in an attempt to identify patients who might benefit from cetuximab, but the findings were not definitive. These data show that adding cetuximab to carboplatin/paclitaxel is not beneficial in all-comers, but it does leave room for some additional analyses.

An important outcome of this study was that patients who received treatment with a carboplatin/paclitaxel backbone achieved a median overall survival of more than 20 months. There is continued debate regarding the efficacy of the weekly carboplatin/paclitaxel regimen compared with cisplatin/etoposide. The overall survival achieved in this trial is similar to that achieved in other large trials with the cisplatin/etoposide backbone and provides support for the weekly carboplatin/paclitaxel approach, although a head-to-head comparison would be needed to make a definitive conclusion.[18]

The addition of erlotinib to radiation therapy was examined in several other trials. In a phase 2, nonrandomized study, erlotinib was added to thoracic radiation for 46 stage III patients.[19] Almost all of the patients were *EGFR*–wild type, limiting the analysis of efficacy results in *EGFR*-mutant NSCLC. Overall survival was approximately 34 months. Interestingly, the few patients with *EGFR* mutations appeared to relapse fairly early. There were no grade 4 or 5 toxicities, which is reassuring as there is some concern that the radiation sensitization of erlotinib could lead to high rates of pneumonitis. Only 3 patients developed grade 3 pneumonitis, and no patients developed grade 4 or 5 pneumonitis. The authors concluded that chemoradiation including erlotinib was fairly well tolerated and associated with a very good overall survival. The results of this study must be viewed with caution because of the limited number of patients, and a larger trial will be needed before this approach can be routinely recommended. The effects of erlotinib will be examined in a newly opened Intergroup trial in the United States of stage III lung cancer patients with known *EGFR* mutations.[20] Patients will be randomized to receive or not receive initial treatment with erlotinib, and then move to standard chemotherapy and radiation, with some additional chemotherapy but no additional erlotinib.

The trial known as TACTIC (A Randomised Placebo-Controlled Multicentre Phase II Trial of Erlotinib Plus Whole Brain Radiotherapy for Patients With Advanced Non-Small Cell Lung Cancer With Multiple Brain Metastases) investigated whole brain radiation with or without erlotinib for patients with multiple brain metastases.[21] This study was small and nonrandomized. The toxicity did not differ substantially between the 2 groups. Although there was more rash with erlotinib than placebo, interestingly, erlotinib was associated with less fatigue than placebo. There has been some concern about keeping patients on erlotinib during whole brain radiation, and this trial provides reassurance regarding the safety of this approach. Unfortunately, erlotinib did not significantly improve outcomes, as both the overall survival and PFS were approximately the same in both arms.

ABSTRACT SUMMARY Final Results of CTONG 0806: A Phase II Trial Comparing Pemetrexed With Gefitinib as Second-Line Treatment of Advanced Non-Squamous NSCLC Patients With Wild-Type EGFR

A multicenter, randomized, open-label, phase 2 trial was conducted to examine the use of pemetrexed vs gefitinib as second-line treatment for advanced, nonsquamous NSCLC (Abstract O15.07). Patients with locally advanced or metastatic, nonsquamous NSCLC had previously been treated with 1 platinum-based chemotherapy. No *EGFR* mutations were present in exons 18 to 21 as determined by direct sequencing. Patients were randomized to receive either pemetrexed (500 mg/m^2) on day 1 every 3 weeks or gefitinib (250 mg) daily. Patients were a median age of 56.5 years (range, 24-78 years), and most were male (64.3%). Approximately half of patients were current or former smokers, and more nonsmokers were assigned to the pemetrexed arm (57.9%) vs the gefitinib arm (40.7%). As assessed by an independent review board, data from 157 evaluable patients showed a PFS of 4.8 months for pemetrexed vs 1.6 months for gefitinib (HR, 0.53; 95% CI, 0.38-0.75; *P*<.001), meeting the primary endpoint. Pemetrexed was superior to gefitinib at all assessments of PFS, including at 4 months (62.0% vs 37.0%; *P*<.001) and 6 months (48.0% vs 27.0%; *P*<.001). The disease control rate was also higher with pemetrexed than gefitinib (61.9% vs 30.8%; *P*<.001). ORR, however, was similar between the 2 arms. The data were consistent with a trend toward superior OS for patients who received pemetrexed (12.4 months vs 9.6 months; *P*=.077). Adequate tumor samples for amplification refractory mutation system (ARMS) were available for 108 patients. In the 76 patients with wild-type EGFR confirmed by ARMS, the median PFS was 4.0 months for pemetrexed (n=35) vs 1.3 months for gefitinib (n=41; 95% CI, 0.26-0.67; HR, 0.42; *P*<.001). Pemetrexed was associated with more nonhematologic (*P*=.003) and total (*P*=.002) grade 3/4 AEs, with no new safety signals raised.

Targeted Agents

NSCLC develops resistance to agents targeting *EGFR* and *ALK*,[22] which has led to treatment challenges in these settings. At the WCLC, there were several exciting presentations about newer drugs that seem to have activity in the resistance setting. In an earlier study from Japan presented at the 2013 ASCO meeting, the novel agent alectinib (formerly known as *CH5424802*) was associated with a response rate of 93% in patients who were crizotinib-naive.[23] At the WCLC, Dr Shirish M. Gadgeel presented data with the compound from patients who developed resistance to crizotinib.[24] The response rate was approximately 60%, which is similar to what has been seen with other novel targeted agents, such as LDK378, in this setting.[25]

Data were presented regarding 2 new *EGFR*-targeted drugs that have activity in patients with known *T790M* mutations. Although the afatinib/cetuximab combination has shown some activity in these patients,[26] it has been difficult to find effective agents. Data on AZD9291 were presented from an ongoing phase 1, dose-escalation trial of patients who had previously received an *EGFR* tyrosine kinase inhibitor.[27] There were no dose-limiting toxicities reported, and 9 of the 18 patients with known *T790M* mutations achieved a response. In another phase 1, dose-escalation trial, a high dose of CO-1686 was associated with a partial response in 6 of 9 patients with a known *T790M* mutation.[28] It is exciting to see activity in patients with tumors harboring *T790M* mutations.

Presentations at the 2013 WCLC included updates of studies examining PD-1 and PD-L1 targeted agents. The PD-1 antibody MK-3475 was reported to have a response rate of approximately 21%; the rate in patients with squamous disease was 33%.[29] No drug-related adverse events of grade 3, 4, or 5 were reported.

Updates on study results with the PD-1 targeted antibody nivolumab included a reported 1-year overall survival rate of 42% and a 2-year rate of 24%.[30] Patients with squamous disease had a slightly better outcome than those with nonsquamous disease. It was encouraging to see long-term responses in some patients.

MPDL3280A targets PD-L1, and in a trial presented by Dr Leora Horn, the 6 patients with high PD-L1 expression by IHC had a high response rate of approximately 80%.[31] As the level of IHC staining decreased, so did the likelihood of response. More activity was seen in patients with a smoking history, as opposed to never smokers, a finding that will be interesting to explore.

Conclusion

Studies from the 15th WCLC offered insight into the management of patients with NSCLC. Few practice-changing trials were presented, but there were data to support further exploration of a maintenance role for *nab*-paclitaxel, as well as preliminary safety and efficacy results with various bevacizumab combination regimens. Unfortunately, the initial promise of customized chemotherapy seems further out of reach with recent results, including those presented at the 15th WCLC by the Spanish Lung Cancer Group. The addition of erlotinib or cetuximab to radiotherapy does not add benefit, but this approach does not appear to be harmful, and it is possible that further work could identify subpopulations that might derive benefit in this setting. Most exciting, though, were the encouraging results from trials with new agents that can overcome resistance to initial *EGFR*- and *ALK*-targeted therapies, and the immune-targeted PD-1 and PD-L1 drugs.

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AVASTIN® (bevacizumab)

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

This is a brief summary of information about AVASTIN. Before prescribing, please see full Prescribing Information.

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.

Avastin, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line Avastin-containing regimen.

Limitation of Use: Avastin is not indicated for adjuvant treatment of colon cancer.
[See *Clinical Studies (14.2)*.]

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 (14.4)*.]

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)*.]

Necrotizing fasciitis including fatal cases, has been reported in patients treated with Avastin; usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Discontinue Avastin therapy in patients who develop necrotizing fasciitis. [See *Adverse Reactions (6.3)*.]

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.