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A SPECIAL MEETING REVIEW EDITION

Highlights in NSCLC From the 2012 Chicago Multidisciplinary Symposium in Thoracic Oncology

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Special Reporting on:

- Weekly nab-Paclitaxel in Combination With Carboplatin as First-Line Therapy For Advanced Non-Small Cell Lung Cancer
- Results of a Global Phase II Study With Crizotinib in Advanced ALK-Positive Non-Small Cell Lung Cancer (NSCLC)
- A Randomized, Open-label, Phase 3, Superiority Study Of Pemetrexed (Pem)+Carboplatin (Cb)+Bevacizumab (B) Followed By Maintenance Pem+B Versus Paclitaxel (Pac)+Cb+B Followed By Maintenance B In Patients (pts) With Stage IIIB Or IV Non-squamous Non-small Cell Lung Cancer (NS-NSCLC)
- The Select Study: a Multicenter Phase II Trial of Adjuvant Erlotinib in Resected Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Non-Small Cell Lung Cancer (NSCLC)
- Clinical Activity and Safety of Anti-PD-1 (BMS-936558, MDX-1106) in Patients (Pts) With Advanced Non-Small-Cell Lung Cancer (NSCLC)
- Clinical Activity of Crizotinib in Advanced Non-Small Cell Lung Cancer (NSCLC) Harboring ROS1 Gene Rearrangement
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PLUS Meeting Abstract Summaries

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Weekly nab-Paclitaxel in Combination With Carboplatin as First-Line Therapy For Advanced Non-Small Cell Lung Cancer

This phase III trial of nab-paclitaxel randomized 1,052 patients with untreated, stage IIIB/IV non–small cell lung cancer (NSCLC) to receive carboplatin and either nab-paclitaxel or solvent-based paclitaxel on 21-day cycles until disease progression or unacceptable toxicity.

Patient-reported neuropathy, neuropathic pain in the hands and feet, and hearing loss were significantly less for patients treated with nab-paclitaxel compared with those treated with solvent-based paclitaxel.[1] Using the functional assessment of cancer therapy (FACT)-Taxane version 4.0 subscales, neuropathy, pain, and hearing were assessed at baseline, on day 1 of each 21-day cycle, and upon completing treatment. A total of 1,031 patients completed FACT-Taxane at baseline, and 987 patients (94%) completed it during follow-up or at the completion of treatment.

The nab-paclitaxel arm was favored for patient-reported neuropathy ($P<.001$), neuropathic pain in the hands and feet ($P<.001$), and hearing loss ($P=.002$) over the solvent-based paclitaxel arm. Physician assessments of neuropathy outcomes were consistent with patient-reported outcomes. The physician-assessed rates of neuropathy were lower with nab-paclitaxel than solvent-based paclitaxel for all grades (46% vs 62%; $P<.001$) and grade 3/4 (3% vs 12%; $P<.001$). Grade 4 peripheral sensory neuropathy was not reported by any patients in the nab-paclitaxel arm. Peripheral neuropathy took 38 days to improve from grade 3 or higher to grade 1 in the nab-paclitaxel arm, compared with 104 days in the solvent-based paclitaxel arm ($P=.238$).

Among the 1,052 NSCLC patients in the phase III study who were randomized to receive carboplatin and either nab-paclitaxel or solvent-based paclitaxel, 15% were aged 70 years or older (74 patients in the nab-paclitaxel arm and 82 patients in the solvent-based paclitaxel arm). Most of these elderly patients were white (71%) and male (72%), had Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores of 1 (73%) and stage IV disease (83%), and were current or former smokers (72%). Patients' baseline characteristics and demographics are summarized in Table 1.

First-line nab-paclitaxel for elderly patients (older than 70 years) was well tolerated and led to improved overall response rates (ORR; 34% vs 24% for solvent-based paclitaxel; $P=.196$; response rate [RR] ratio=1.385) and progression-free survival (PFS; median 8.0 vs 6.8 months for solvent-based paclitaxel; $P=.134$; hazard ratio [HR]=0.687).[2] Overall survival (OS) was significantly

A Randomized Phase II Study of Pazopanib or Placebo in Combination With Erlotinib in Patients With Advanced Non-Small-Cell Lung Cancer

Pazopanib plus erlotinib improved PFS when compared with erlotinib plus a placebo (median 2.60 vs 1.81 months; HR=0.59; 95% CI, 0.43–0.83; $P=.0016$) in this randomized, placebo-controlled, phase II study of previously treated patients with stage IIIB or IV NSCLC and ECOG PS of 0 or 1 (Abstract 13). The trial met its goal of a 50% improvement in PFS. Unfortunately, treatment with pazopanib did not improve OS (6.8 months vs 6.7 months with placebo and erlotinib; HR=1.1; 95% CI, 0.77–1.55; $P=.61$). Several biomarker-defined subgroups did have PFS advantages when treated with pazopanib and erlotinib. Grade 3/4 hematologic toxicity was less than 4% in both arms. Severe nonhematologic AEs were diarrhea (15% with pazopanib vs 9% with placebo), fatigue (21% with pazopanib vs 15% with placebo), and proteinuria (5% with pazopanib vs 0% with placebo). Pazopanib was associated with a greater frequency of elevated hepatic enzymes (occurring in up to 5% of patients), and this condition reversed when therapy was stopped.

longer with nab-paclitaxel (median, 19.9 months) than with solvent-based paclitaxel (median, 10.4 months; *P*=.009; HR=0.583; Figure 1) in elderly patients with advanced NSCLC.

The adverse events (AEs) were comparable among patients aged 70 years or older and patients younger than 70 years. When the nab-paclitaxel and solvent-based paclitaxel arms were compared, the nab-paclitaxel arm had less grade 3 or 4 neutropenia (54% vs 74%; *P*<.05) and neuropathy (7% vs 23%; *P*<.05), and increased thrombocytopenia (23% vs 14%; *P*=not significant) and anemia (23% vs 10%; *P*<.05). These rates in elderly patients were similar to those observed in the intent-to-treat (ITT) population. Among the 99% of elderly patients who completed the FACT-Taxane assessment at baseline, significant treatment effects occurred that favored nab-paclitaxel over solvent-based paclitaxel for neuropathy (*P*<.001), pain in hands and feet (*P*<.001), hearing loss (*P*=.022), and edema (*P*=.004).

Among the 1,052 randomized patients in the phase III study, 518 had adenocarcinoma histology, 450 had squamous cell carcinoma (SCC) histology, and 84 patients had either large cell carcinoma (LCC) or carcinoma that was not otherwise specified (NOS).[3] The patients with SCC had a higher ORR with nab-paclitaxel (41%) than with solvent-based paclitaxel (24%; *P*<.001; RR ratio=1.680). Both arms of patients with SCC had similar PFS (5.6 vs 5.7 months; *P*=.245; HR=0.865). Nab-paclitaxel trended toward prolonging OS by more than 1 month (10.7 vs 9.5 months; *P*=.284; HR=0.890).

Among patients with LCC or NOS-NSCLC, the nab-paclitaxel arm had a higher ORR (26%) than the solvent-based paclitaxel arm (15%; *P*=.208; RR ratio=1.729), longer PFS (6.4 vs 4.2 months; *P*=.061; HR=0.565), and similar OS (10.5 vs 11.2 months; *P*=.702; HR=1.100). Among patients with adenocarcinoma, nab-paclitaxel was as effective as solvent-based paclitaxel for ORR (26% vs 27%; *P*=.814; RR

Table 1. Baseline Patient Demographics and Clinical Characteristics

	nab-Paclitaxel (n=521)		Solvent-Based Paclitaxel (n=531)		All (N=1,052)	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Age, years						
Median	60		60		60	
Range	28–81		24–84		24–84	
<70	447	86	449	85	896	85
≥70	74	14	82	15	156	15
Sex						
Male	392	75	397	75	789	75
Female	129	25	134	25	263	25
Race						
Asian	79	15	80	15	159	15
African heritage	12	2	8	2	20	2
White	416	80	433	82	849	81
Hispanic, Latino	11	2	5	<1	16	2
Other	3	<1	5	<1	8	<1
Country						
Australia	5	<1	9	2	14	1
Canada	21	4	23	4	44	4
Japan	74	14	75	14	149	14
Russia	238	46	231	44	469	45
Ukraine	120	23	135	25	255	24
United States	63	12	58	11	121	12
ECOG PS						
0	133	26	113	21	246	23
1	385	74	416	78	801	76
2	3	<1	2	<1	5	<1
Histology						
Adenocarcinoma	254	49	264	50	518	49
Squamous cell carcinoma	229	44	221	42	450	43
Large cell carcinoma	9	2	13	2	22	2
Other	29	6	33	6	62	6
Stage at random assignment						
IIIB	108	21	110	21	218	21
IV	413	79	421	79	834	79
Prior therapy						
Radiation therapy	39	7	50	9	89	8
Chemotherapy	14	3	13	2	27	3
Smoking status	519*		526*		1,045*	
Never smoked	137	26	144	27	281	27
Smoked and quit	168	32	148	28	316	30
Smoked and still smokes	214	41	234	44	448	43

ECOG=Eastern Cooperative Oncology Group; PS=performance status.

*Few missing values.

Data from Socinski MA et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. *J Clin Oncol.* 2012;30:2055-2062.

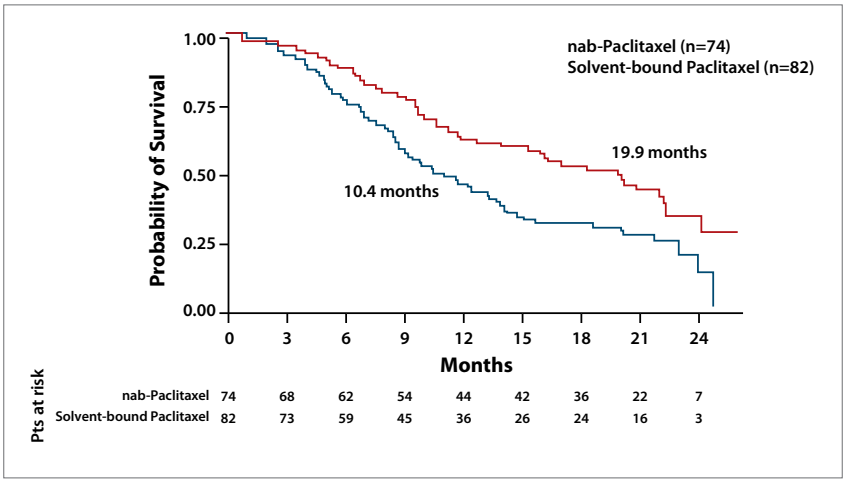

Figure 1. Improved overall survival with nab-paclitaxel versus solvent-based paclitaxel in elderly patients.

Data from Socinski MA et al. Weekly nab®-paclitaxel in combination with carboplatin as first-line therapy in elderly patients (pts) with advanced non-small cell lung cancer (NSCLC). Paper presented at: the 2012 Chicago Multidisciplinary Symposium in Thoracic Oncology; September 6-8, 2012; Chicago, IL. Abstract 109.

ratio=0.966), PFS (6.9 months in both arms; *P*=.944; HR=0.991), and OS (13.9 vs 13.6 months; *P*=.639; HR=0.949). Like the ITT population, nab-paclitaxel treatment resulted in lower rates of grade 3 or 4 neuropathy and higher rates of anemia and thrombocytopenia than solvent-based paclitaxel in these histologic groups. Grade 3 or 4 neutropenia was lower with nab-paclitaxel than with solvent-based paclitaxel in patients with SCC (43% vs 51%; *P*=.103) and adenocarcinoma (49% vs 64%; *P*<.001), but not LCC or NOS (62% vs 53%; *P*=.500) histology.

Baseline patient characteristics and clinical treatment preferences differ by geographic region in large, international trials of advanced NSCLC. An analysis by region of this phase III trial included data from 1,038 patients.[4] The patients were from Russia/Ukraine (n=724; 69%), North America (n=165; 16%), and Japan (n=149; 14%). Compared with the cohort from Russia/Ukraine, the cohorts from North America and Japan were generally older (median age, 65 years vs 58 years in Russia/Ukraine), had primarily nonsquamous histology (56% in North America, 77% in Japan, and 44% in Russia/Ukraine), and had a history of smoking (91% in North America, 76% in Japan, and 68% in Russia/Ukraine). More elderly patients (aged 70 years or older) were included in the North American (33%) and Japanese (21%) cohorts than the Russian/Ukrainian (9%) cohort.

For all 3 regions, ORR favored nab-paclitaxel over solvent-based paclitaxel in North America (25% vs 22%; RR ratio=1.125; *P*=.675), Japan (35% vs 27%; RR ratio=1.318; *P*=.263), and Russia/Ukraine (34% vs 26%; RR ratio=1.327; *P*=.014). Response rates were not affected by region, according to multivariate analysis.

Region did affect OS. For nab-paclitaxel versus solvent-based paclitaxel, median OS was 12.7 versus 9.8 months (*P*=.008) in North America, 11.0 versus 11.1 months (*P*=.834) in Russia/Ukraine, and 16.7 versus 17.2 months (*P*=.814) in Japan. The regions had variation in the number of treatment cycles (5 in North America, 4 in Japan, and 6 in Russia/Ukraine) and in the proportion of patients receiving 6 or fewer cycles of nab-paclitaxel (86% in North America, 89% in Japan, and 60% in Russia/Ukraine). Japan had the highest use of second-line therapy (85%), followed by North America (69%) and Russia/Ukraine (44%).

The safety and efficacy of nab-paclitaxel was analyzed among the 53 patients whose creatine clearance was less than or equal to 50 mL/min at baseline (n=26 in the nab-paclitaxel arm and n=27 in the solvent-based paclitaxel arm).[5] These patients had a median age of 70 years in both treatment arms. The rates of grade 1 creatinine elevation were lower in patients receiving nab-paclitaxel (0%) than in those receiving solvent-based paclitaxel (7%; *P*=.161). The rates of grade 3 or higher AEs were lower for the patients receiving nab-paclitaxel (62%) than for those receiving solvent-based paclitaxel (81%). The patients in the nab-paclitaxel arm did not experience any grade 3 or higher sensory neuropathy, although 19% of patients in the solvent-based paclitaxel arm did (*P*=.051). The nab-paclitaxel arm had a lower rate of grade 3 or higher neutropenia (44%) than the solvent-based paclitaxel arm (77%; *P*=.023). Notably, grade 3 or higher anemia and thrombocytopenia were higher in the nab-paclitaxel arm (32% and 28%) than in the solvent-based paclitaxel arm (15% and 4%; *P*=.193 and *P*=.022, respectively). The rates of grade 3 or higher fatigue were lower in the nab-paclitaxel arm (8%) than in the solvent-based paclitaxel arm (22%; *P*=.250).

Among the patients with renal impairment, those in the nab-paclitaxel arm had a median paclitaxel dose intensity of 83.33 mg/m^2/week and a median of 4 cycles, while those in the solvent-based paclitaxel arm had a median dose of 60.43 mg/m^2/week and a median of 5 cycles. The nab-paclitaxel arm had a higher ORR of 31% versus 19% for the solvent-based paclitaxel arm (RR ratio=1.662; *P*=.300). The nab-paclitaxel arm had a longer median PFS than the solvent-based paclitaxel arm (6.0 months vs 4.7 months; HR=0.607; *P*=.238), and a longer median OS (9.7 months vs 9.3 months; HR=0.824; *P*=.576).

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Results of a Global Phase II Study With Crizotinib in Advanced ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

In lung adenocarcinomas, the most common mutations involve KRAS and EGFR, although approximately 35% of lung adenocarcinomas have unknown mutations. Gene rearrangements of anaplastic lymphoma kinase (ALK) have been identified in approximately 3–5% of NSCLCs, and these occur most frequently in adenocarcinomas. Crizotinib (PF-02341066) is an oral ALK inhibitor that demonstrated a 61% response rate and 10-month median PFS in a phase I study.[1]

Updated data from the subsequent phase II study of crizotinib in patients with previously treated, advanced ALK-positive NSCLC (NCT0032451) were presented.[2] This phase II, single-arm, multicenter study has enrolled approximately 1,100 patients, and enrollment is ongoing. The key eligibility criteria are ALK-positive NSCLC, as determined by the central laboratory; ECOG PS of 0–3; and history of 1 or more prior lines of chemotherapy. Patients with stable or controlled brain metastases are allowed to enroll. Enrolled patients receive continuous dosing with oral crizotinib 250 mg twice daily. The primary endpoints are ORR and safety/tolerability. Of the 259 patients who were evaluable for response, 4 (2%) had a complete response (CR), 151 (58%) had a partial response (PR), 69 (27%) had stable disease (SD), and 19 (7%) had progressive disease (PD). The median PFS was 8 months (95% CI, 7–10 months), and 28% of patients were in follow-up for progression. Figure 2 shows the best response of indicator lesions in 240 response-evaluable patients, excluding those with early death, indeterminate response, and non-measurable disease.

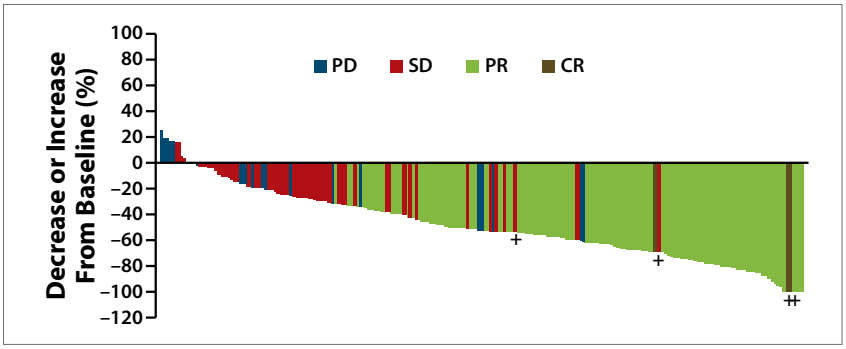

Figure 2. Best response of indicator lesions in 240 response-evaluable patients from the mature population in a phase II study of crizotinib.

CR=complete response; PD=progressive disease; PR; partial response; SD=stable disease.
Data from Riely GJ et al. Results of a global phase II study with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC). Paper presented at: the 2012 Chicago Multidisciplinary Symposium in Thoracic Oncology; September 6-8, 2012; Chicago, IL. Abstract 3.

A total of 18 patients with asymptomatic, non-irradiated brain metastases were evaluable for both brain and systemic disease. Of these 18 patients, 2 (11%) had a CR, 2 (11%) had a PR, 12 (67%) had SD, and 2 patients (11%) had PD.

The most frequent treatment-related AEs, which were mostly grade 1 and 2, were visual effects (50%), nausea (46%), vomiting (39%), and diarrhea (35%). Treatment-related serious AEs were reported for 29 patients (6.6%). They included dyspnea and pneumonitis (4 patients each, 0.9%), as well as febrile neutropenia and renal cysts (2 patients each, 0.5%).

The researchers concluded that crizotinib treatment led to a response rate of 60% and median PFS of 8 months. Crizotinib continued to show a good safety profile in patients with previously treated ALK-positive advanced NSCLC. The researchers noted that clinically meaningful improvement was observed in global quality of life, and in such lung cancer symptoms as fatigue, cough, dyspnea, and chest pain. The data are consistent with the efficacy and safety findings previously reported. The data further support the use of crizotinib in patients with ALK-positive lung cancer, and provide strong evidence for its use as standard of care for advanced ALK-positive NSCLC.

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A Randomized, Open-label, Phase 3, Superiority Study Of Pemetrexed (Pem)+Carboplatin (Cb)+Bevacizumab (B) Followed By Maintenance Pem+B Versus Paclitaxel (Pac)+Cb+B Followed By Maintenance B In Patients (pts) With Stage IIIB Or IV Non-squamous Non-small Cell Lung Cancer (NS-NSCLC)

Platinum-based chemotherapy combinations are recommended for first-line treatment of advanced NSCLC.[1] For patients with nonsquamous NSCLC in the United States, 2 regimens are widely used because they improve survival. The regimen of paclitaxel, carboplatin, and bevacizumab, followed by bevacizumab maintenance, improves response rates, PFS, and OS, and it is approved for first-line treatment of nonsquamous NSCLC.[2] The other regimen, cisplatin and pemetrexed, is preferred because of its non-inferiority to cisplatin and gemcitabine and its improved toxicity profile.[3] The regimen of cisplatin and pemetrexed followed by continuation maintenance therapy with pemetrexed also led to improvements in PFS and OS.[4,5] Finally, the previously reported phase II single-arm study that combined pemetrexed, carboplatin, and bevacizumab for 6 cycles, followed by maintenance with pemetrexed and bevacizumab, demonstrated a promising OS of 14.1 months and PFS of 7.8 months.[6]

These findings led to the PointBreak (A Randomized, Open-label, Phase 3, Superiority Study Of Pemetrexed [Pem]+Carboplatin [Cb]+Bevacizumab [B] Followed By Maintenance Pem+B Versus Paclitaxel [Pac]+Cb+B Followed By Maintenance B In Patients [pts] With Stage IIIB Or IV Non-squamous Non-small Cell Lung Cancer [NS-NSCLC]) trial, which was designed as a superiority study to compare a treatment arm of pemetrexed, carboplatin, and bevacizumab followed by maintenance with pemetrexed and bevacizumab (the pemetrexed arm) to an arm with paclitaxel, carboplatin, and bevacizumab followed by bevacizumab maintenance (the paclitaxel arm).[7] Patients were randomized 1:1 to the 2 study arms. The study was conducted in the United States at 147 sites. It was designed to compare survival from time of initial therapy for patients with stage IIIB or IV nonsquamous NSCLC, as defined by the American Joint Committee on Cancer's sixth edition of their staging manual.[8] Importantly, patients with stable, treated brain metastases were allowed to enroll. Other inclusion criteria were no prior systemic therapy for lung cancer, PS of 0 or 1, and stage IIIB or IV nonsquamous NSCLC. Exclusionary criteria were pre-existing neuropathy of grade 1 or higher, along with uncontrolled pleural effusions.

Dacomitinib (D) Versus Erlotinib (E) in Patients (pt) With EGFR-Mutated (mu) Advanced Non-Small Cell Lung Cancer (NSCLC): Analyses From a Randomized, Phase 2 Trial

Among EGFR-mutated advanced NSCLC patients receiving second- or third-line treatment, dacomitinib had superior PFS compared with erlotinib (HR=0.46; 95% CI, 0.18–1.18; 2-sided *P*=.098). Both arms had a median PFS of 32 weeks (95% CI, 17–80 weeks for dacomitinib and 11–48 weeks for erlotinib). This subset analysis is the first to compare a pan-HER tyrosine-kinase inhibitor, which acts irreversibly across the kinase-active members of the HER family, to a selective, reversible EGFR tyrosine-kinase inhibitor (Abstract 2). Among the 188 patients enrolled in this randomized, phase II trial, EGFR mutations occurred in 19 patients receiving dacomitinib and in 11 patients receiving erlotinib. The ORR was 58% (95% CI, 33.5–79.7) for patients treated with dacomitinib and 36% (95% CI, 10.9–69.2) for patients treated with erlotinib (*P*=.26). Among the patients with mutations in exon 19 of EGFR (8 in each arm of the trial), the PFS HR (dacomitinib vs erlotinib) was 0.27 (95% CI, 0.076–0.94; 2-sided *P*=.028). These patients had a median PFS of 77 weeks (95% CI, 32.3–NA) with dacomitinib and 24 weeks (95% CI, 11.4–NA) with erlotinib. The small sample size does not allow definitive conclusions regarding whether mutations in exon 19 are predictive of treatment effects. The most frequently reported AEs were diarrhea, acneiform dermatitis, stomatitis, decreased appetite, mucosal inflammation, and paronychia. These events were mostly grade 1/2, and they were manageable with standard supportive care. One grade 4 treatment-related AE occurred with dacomitinib, which was increased blood creatinine.

Survival was calculated from the time of randomization through induction, maintenance, and onward. The primary objective was to demonstrate a 20% improvement in survival for patients treated in the pemetrexed arm compared with the paclitaxel arm. This objective required 676 events in 900 patients for 80% power and a 1-sided error of 0.025.

The trial was also designed to evaluate PFS, time to PD, ORR, safety, and patient-reported outcomes. (The patient-reported outcomes will be presented at a forthcoming meeting.) The prespecified but exploratory analyses were OS, PFS in the maintenance population, and PFS without grade 4 toxicity. For the endpoint of PFS without grade 4 toxicity, an event was defined as either PD or the occurrence of grade 4 toxicity.

Enrollment in the study began on December 30, 2008, and the database log occurred on May 17, 2012. A total of 1,259 patients enrolled so that 939 patients could be randomized, which eventually resulted in 292 patients on maintenance with pemetrexed and bevacizumab and 298 patients on maintenance with bevacizumab alone. The vast majority of patients who discontinued the study did so because of PD.

Treatment arms were well balanced. Median age was 75.0 years in the pemetrexed arm and 72.4 years in the paclitaxel arm. Notably, African-American enrollment was 10% across the entire study, which aligns well with US census data and differs from the 5% representation among the current trials reported at the 2012 meeting of the American Society of Clinical Oncology (ASCO).

From the time of randomization to initial therapy, PFS was improved in the pemetrexed arm (median 6.0 months in the pemetrexed arm vs 5.6 months in the paclitaxel arm; HR=0.83; *P*=.012). Both arms had similar response rates (34.1% with pemetrexed and 33.0% with paclitaxel), which were consistent with previously recorded results. Almost all subgroups slightly favored pemetrexed, although the 172 patients with other or indeterminate histology had PFS that appeared to favor paclitaxel (HR=1.19), without reaching significance.

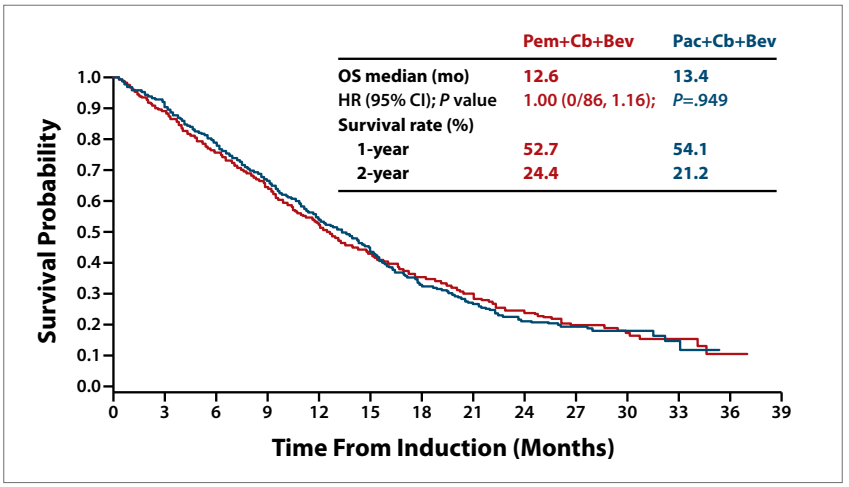

Figure 3. Kaplan-Meier overall survival curves from the time of randomization in the intent-to-treat population.

Bev=bevacizumab; Cb=carboplatin; HR=hazard ratio; OS=overall survival; Pem=pemetrexed.
Data from Patel JD et al. A randomized, open-label, phase III, superiority study of pemetrexed (Pem) + carboplatin (Cb) + bevacizumab (Bev) followed by maintenance Pem + Bev versus paclitaxel (Pac)+Cb+Bev followed by maintenance Bev in patients with stage IIIB or IV non-squamous non-small cell lung cancer (NS-NSCLC). Paper presented at: the 2012 Chicago Multidisciplinary Symposium in Thoracic Oncology; September 6-8, 2012; Chicago, IL. Abstract LBPL1.

From the time of randomization in the ITT population, the Kaplan-Meier OS curves are superimposable for the 2 arms (Figure 3). The HR is 1.00 (95% CI, 0.86–1.16; *P*=.949). The pemetrexed arm did not have improvement. Similarly, OS was not affected by subgroup, although the small number of patients with large cell histology seemed to have improved OS with pemetrexed (HR=0.53), and those with other or indeterminate histologies seemed to have improved OS with paclitaxel (HR=1.36).

Although the trial was designed to evaluate OS improvements in the ITT populations from the time of randomization prior to induction therapy, a prespecified and exploratory analysis of PFS in the maintenance population was also planned. Patients who had at least stable or responsive disease during the 4 cycles of induction demonstrated PFS of 8.6 months in the pemetrexed arm (n=292) and 6.9 months in the paclitaxel arm (n=298). This population had demographics that were very similar to the ITT population. For patients who received maintenance therapy, the OS was 17.7 months in the pemetrexed arm and 15.7 months in the paclitaxel arm. Among the group of patients who did not go on to receive maintenance—largely because of PD or toxicity—the median OS was only 4.6 months in the pemetrexed arm and 6.1 months in the paclitaxel arm.

Toxicities related to the study drugs were evaluated among patients who received at least 1 dose of the study drug. Both regimens were tolerable overall. However, the toxicity parameters had significant differences. Pemetrexed was associated with significantly more anemia (grade 1/2, 31.0% for pemetrexed vs 24.4% for paclitaxel; grade 3/4, 14.5% vs 2.7%, respectively) and thrombocytopenia (grade 1/2, 17.9% vs 17.2%, respectively; grade 3/4, 23.3% vs 5.6%, respectively), whereas paclitaxel was associated with more neutropenia (grade 3/4, 40.6% for paclitaxel vs 25.8% for pemetrexed) and febrile neutropenia (grade

Accuracy of Fine Needle Aspiration and Core Lung Biopsies to Predict Histology in Patients With Non Small Cell Lung Cancer

Although treatment decisions in NSCLC are guided by histologic diagnosis, the overall concordance rate between preoperative and final histologic subtype is only 67.2% (80/119 patients with NSCLC). Such data guide the treatment of patients with nonsquamous NSCLC, who are treated exclusively with pemetrexed and bevacizumab. This retrospective review of 295 lobectomies in 117 patients at the University of Arkansas between 2002 and 2011 sought to determine how accurately the histologic subtype of primary NSCLC can be determined by fine needle aspiration and core lung biopsies (Abstract LBOA2). The included histologic subtypes were squamous, nonsquamous, and adenosquamous. Patients had a final diagnosis of primary NSCLC and a preoperative biopsy performed by bronchoscopy or computed tomography (CT) guidance. From preoperative to final histologic subtype, the nonsquamous histology increased from 43% to 56%, squamous from 31% to 36%, and adenosquamous from 2% to 8%. A total of 29 preoperative biopsies did not specify a histologic subtype, and 10 preoperative biopsies changed histologic subtype. The most common change from preoperative subtype to final histologic subtype was from NSCLC to nonsquamous (11 patients). Data on pemetrexed for nonsquamous NSCLC were first presented at the 2007 ASCO annual meeting, but concordance rates were not significantly different before and after pemetrexed data were presented and published. Further, concordance rates did not have statistically significant differences based on tumor location (P=.630), type of biopsy procedure (P=.773), preoperative stage (P=.995), postoperative stage (P=.443), or differentiation (P=.061). No factors have been identified to predict which patients are at higher risk for an inaccurate histologic diagnosis.

3/4, 4.1% vs 1.4%, respectively). A total of 18 grade 5 AEs occurred. Importantly, none of the grade 5 hemorrhages were related to grade 3 or 4 thrombocytopenia, which is a complication of post-discontinuation therapies (treatment at second-line or progression and beyond). Only 53% of patients in the pemetrexed arm went on to receive second-line therapies or beyond, whereas 59% of patients in the paclitaxel arm went on to receive second-line therapies or beyond.

In conclusion, the primary endpoint of superior OS was not met in this trial. The HR was 1, and the lines were superimposable. The efficacy, response rates, and survival were similar to previously published data for paclitaxel, carboplatin, and bevacizumab followed by bevacizumab maintenance.[2] Patients who received pemetrexed, carboplatin, and bevacizumab followed by maintenance therapy had superior PFS compared with those who received paclitaxel, carboplatin, and bevacizumab followed by maintenance therapy (6.0 months vs 5.6 months). In a prespecified, exploratory, noncomparative analysis of the maintenance population, OS was 17.7 months in the pemetrexed arm and 15.7 months in the paclitaxel arm. The regimens have different toxicity profiles, but both are considered tolerable.

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The Select Study: a Multicenter Phase II Trial of Adjuvant Erlotinib in Resected Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Non-Small Cell Lung Cancer (NSCLC)

Adjuvant chemotherapy for NSCLC results in modest improvements, with an OS benefit of approximately 5–10% seen at 5 years, which is predominantly in stage II and III NSCLC. However, many patients still relapse after treatment with adjuvant chemotherapy.[1]

In the metastatic setting, tumors with mutations activating epidermal growth factor receptor (EGFR) are very sensitive to EGFR inhibitors.[2,3] A retrospective cohort study showed a 2-year disease-free survival (DFS) of 89% in patients whose EGFR-mutant tumors were treated with erlotinib or gefitinib versus 72% in untreated patients.[4] The Select study of adjuvant erlotinib was a single-arm, phase II study in patients with surgically resected, stage I–III NSCLC whose tumors harbored EGFR mutations.[5] Patients received adjuvant erlotinib 150 mg daily for 2 years. They were scanned by CT every 6 months for 3 years, and then annually for years 4 and 5 during the observation period. The primary endpoint was DFS, and the 2-year target was 86%. The secondary endpoints were OS, safety, and tolerability.

The characteristics among the 36 enrolled patients were as expected for a trial that selected patients with EGFR-mutant tumors. Most patients were women (75%), never-smokers (56%), and non-Asian (89%), since the trial was conducted in the United States. More than half of patients had stage I disease (53%; stage IB, 39%; stage IA, 14%). Disease stages II and III were less prevalent (19% and 28%, respectively).

Mutation analysis found that 22 patients had EGFR exon 19 deletions (61%), 13 patients had L858R mutations (36%), and 1 patient had the L861Q mutation (3%). All types of EGFR-sensitizing mutations were allowed in the study, except for such mutations as exon 20 insertions or T790.

After a median follow-up of 2.7 years, the DFS rate was 94% (95% CI, 80–90%). Only 2 patients died of recurrent disease, and all other patients remained alive.

The AEs were as expected for adjuvant erlotinib and predominantly included rash (89%), diarrhea (78%), and fatigue (61%). Dose reductions occurred due to rash, transaminitis, diarrhea, fatigue, hyperbilirubinemia, and urticaria. Doses were reduced to 100 mg daily for 8 patients (22%) and 50 mg daily for 5 patients (14%). A total of 69% of patients completed more than 90% of the full 2 years of treatment. A total of 11 patients (31%) discontinued before they had been treated for 2 years. Among the patients who stopped the study, some did so because of toxicities (n=6), which were mainly diarrhea, rash, or fatigue. Other reasons for going off study were patient preference (n=3), travel, and, for 1 patient, the development of incidental prostate cancer. One patient came off study due to recurrence.

Among the 12 patients who had progressed to date, some completed

Evaluation of VeriStrat in the Randomized, Placebo-Controlled, Phase II Trial of Erlotinib and High-Dose Celecoxib in Advanced Non-Small Cell Lung Cancer

VeriStrat is a commercially available, pretreatment serum test that classifies NSCLC patients as likely to have "Good" or "Poor" outcomes after treatment with erlotinib. A limited population of patients with NSCLC receives a significant benefit from EGFR inhibitor therapy. When EGFR is activated, COX-2 expression is upregulated, which can increase the expression of EGFR ligands. This study enrolled 107 patients with stage IIIB or IV NSCLC. Patients were randomized to receive erlotinib and high-dose celecoxib or erlotinib and placebo, and 96 samples were classified by VeriStrat (Abstract LBOA1). The correlation between VeriStrat classification and durable clinical response was significant in the combined arms (P=.010) and in the arm of patients receiving erlotinib and high-dose celecoxib (P=.008). ORR was significantly correlated with VeriStrat status in the combined arm (P=.002). VeriStrat classification was not significantly correlated with mutation status. Patients whose VeriStrat classification was Good had a longer PFS (P<.0001) and OS (P<.0001) in the erlotinib and high-dose celecoxib arm, and a longer OS (P=.001) in the erlotinib and placebo arm. When VeriStrat Good status was stratified by EGFR mutation status, patients with wild-type EGFR had improved PFS from the addition of high-dose celecoxib, while those with EGFR mutations did not likely benefit from the high-dose celecoxib. VeriStrat may be useful to identify NSCLC patients with Good classification who will benefit from combining high-dose celecoxib with erlotinib.

Ablative Local Therapy Extends the Clinical Benefit of Crizotinib in ALK-Positive Lung Cancer

Among ALK-positive NSCLC patients treated with crizotinib who had oligoprogression, treatment with ablative local therapy caused minimal toxicity and allowed patients to gain 9 months of additional clinical benefit from crizotinib, along with improved OS (Abstract 21). Oligoprogression was defined as the emergence of 5 or fewer sites of disease that were resistant to crizotinib and outside the central nervous system. This approach of treating disease that is oligoprogressive and crizotinib-resistant departs from the traditional method of changing systemic therapy at the first sign of progression. The study enrolled 38 patients with metastatic ALK-positive NSCLC. The patients were followed by surveillance scans every 6–8 weeks. When oligoprogression was found, ablative local therapy was performed through either hypofractionated radiotherapy or surgery. If the patient was still receiving clinical benefit, crizotinib was continued. Clinical benefit was defined as sustained control of other disease sites outside the central nervous system and minimal toxicity. Disease progression in the central nervous system was treated with local therapy. Crizotinib was discontinued if toxicity was unacceptable or if the disease progressed beyond oligoprogression. Patients were followed for a median of 19.6 months (range, 2–32 months). Of the 10 patients who experienced oligoprogression, it occurred at a median of 6.5 months (range, 2–24 months) after crizotinib was initiated. The clinical benefit from crizotinib was extended by ablative local therapy by 9.2 months. Among the 10 patients who received ablative local therapy, the median time on crizotinib was 17.4 months, while the other 28 patients received crizotinib for a median of 12.6 months. Additionally, the 1-year actuarial OS was 100% for the patients who received crizotinib and ablative local therapy, compared with 70% for those who received crizotinib alone (P=.002).

2 years of therapy and some did not. Only 1 patient progressed while on adjuvant therapy. The remainder progressed 3–24 months after finishing treatment with adjuvant erlotinib. Sites of progression varied, with some patients having a solitary recurrence in the brain, lung, or bone. Others had multifocal recurrence in a metastatic fashion. Among evaluated patients who received erlotinib after they progressed, all responded and all remained on erlotinib at the time of the study presentation, which ranged from 4 months to 26 months after recurrence.

Treatment with adjuvant erlotinib was feasible for patients with EGFR-mutated NSCLC. Many patients required a dose reduction or discontinued treatment. The primary endpoint of 2-year DFS was met at a rate of 94%. Adjuvant erlotinib seems to have, at the very least, a cytostatic effect on micrometastatic disease, as only 1 patient recurred during treatment. Although patients recurred at various times after treatment, a possible genetic mechanism of resistance was identified in only 2 of the 8 recurrent tumors. All evaluable patients who restarted erlotinib for metastatic disease had a response.

This trial has subsequently expanded from 36 patients to a total of 100 patients in order to permit subgroup analysis by stage. Enrollment is complete, and final results of the subgroup analysis are expected within a few years.

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Clinical Activity and Safety of Anti-PD-1 (BMS-936558, MDX-1106) in Patients (Pts) With Advanced Non-Small-Cell Lung Cancer (NSCLC)

The programmed death-1 (PD-1) pathway is important in T-cell activation, and its role in NSCLC requires further study. Expression of PD-1 on tumor infiltrating lymphocytes decreases cytokine production and effector function.[1,2] The expression of PD-L1 has been noted in NSCLC.[3] Increased PD-1 expression on tumor cells is correlated with an increased number of tumor-infiltrating lymphocytes in the same region.[4]

Activated T cells express the PD-1 co-inhibitory receptor, which is blocked by the fully human, monoclonal antibody BMS-936558.[5] This interim analysis demonstrated that BMS-936558 mediates anti-tumor activity in heavily pretreated patients with advanced NSCLC.[6] The analysis was conducted in a large, phase I, multi-dose study that administered the antibody intravenously once every 2 weeks for an 8-week treatment cycle. The doses were 0.1, 1, 3, or 10 mg/kg during the dose escalation and cohort expansion phases. The study included patients with advanced melanoma, renal cell cancer, NSCLC, colorectal cancer, and prostate cancer. These patients had PD and were heavily pretreated with up to 5 prior regimens. Patients received 4 doses of treatment per cycle for up to 12 cycles. Patients remained on study if they had a response, SD, or even progression or clinical stability; treatment lasted for up to 96 weeks. Patients went off study if they had unacceptable toxicity, confirmed PD, or complete response. The primary objective was to assess safety and tolerability when the antibody was administered once every 2 weeks. Secondary objectives included assessing anti-tumor activity and evaluating pharmacodynamics. The initial activity observed in the dose-escalation portion of the study (particularly in NSCLC) led to enrolling the expansion cohorts at 3 different dose levels. Equal numbers of patients with NSCLC were randomized between 3 dose levels of 1, 3, or 10 mg/kg, for a total of 32 patients on each dose level. The study enrolled equal numbers of patients with squamous and nonsquamous histology. A total of 122 patients with NSCLC were followed for safety, and 76 patients with NSCLC were followed for clinical activity. This analysis included patients treated through February 2012 who had been evaluated or followed for at least 6 months.

The safety population of 120 new patients had a mean age of 65 years, and most were men (61%). Patients were divided between squamous cell histology (39%) and nonsquamous cell histology (60%). Most patients had good ECOG PS (0 for 34 patients, 1 for 83 patients, 2 for 2 patients, and not reported for 3 patients). The number of prior therapies was 1 for 18 patients, 2 for 31 patients, 3 for 27 patients, and 4 or more for 40 patients. Platinum-based therapies had been administered in 94% of patients, and 34% had received a prior tyrosine kinase inhibitor.

BMS-936558 was generally well tolerated. AEs occurred in 64% of NSCLC patients. The maximum tolerated dose was not found. At the doses of up to 10 mg/kg included in this study, no relationship was apparent between dose and AE frequency. In the NSCLC patients, the common drug-related AEs were fatigue (18%), decreased appetite (10%), anemia (8%), nausea (7%), pyrexia (6%), and diarrhea (6%).

Table 2. Clinical Activity of BMS-936558 in Patients With NSCLC

Population	Dose (mg/kg)	Patients n	ORR n (%)	Response Duration (months)	Stable Disease ≥24 Weeks n (%)	PFSR at 24 Weeks (%)
All NSCLC	1–10	76	14 (18)	1.9+ to 30.8+	5 (7)	26
NSCLC	1	18	1 (6)	9.2+	1 (6)	16
	3	19	6 (32)	1.9+ to 30.8+	2 (11)	41
	10	39	7 (18)	3.7–14.8+	2 (5)	24

NSCLC=non–small cell lung cancer; ORR=overall response rate; PFSR=progression-free survival rate.
ORR was assessed using modified Response Evaluation Criteria In Solid Tumors (RECIST) v1.0 (3 NSCLC patients had a persistent reduction in baseline target lesions in the presence of new lesions but were not classified as responders for the ORR calculation).
Data from Brahmer J et al. Clinical activity and safety of anti-PD-1 (BMS-936558, MDX-1106) in patients (Pts) with advanced non-small-cell lung cancer (NSCLC). Paper presented at: the 2012 Chicago Multidisciplinary Symposium in Thoracic Oncology; September 6-8, 2012; Chicago, IL. Abstract 4.

Clinical Behavior of Lung Cancers Harboring EGFR Exon 20 Insertions

While patients with EGFR exon 20 insertions have similar clinical characteristics as other patients with EGFR mutations, they tend to do poorly on tyrosine kinase inhibitors and have a shorter survival. The subset of EGFR exon 20 insertions is the third most common family of EGFR mutations in NSCLC, representing 9% of EGFR-mutant lung cancers. Patients with EGFR exon 20 insertions are an attractive population for trials of new targeted therapies. This study reviewed an institutional database of 951 patients with NSCLC who underwent EGFR sequencing (Abstract 10). Of these, 233 patients had an EGFR mutation, and 25 (11%, or 2.6% of all patients) had an insertion in exon 20. The patients with insertions in exon 20 and those with other EGFR mutations were more often never-smokers (56% and 53%) and Asian (16% and 12%) than the patients with wild-type EGFR (21% never-smokers, $P<.001$ for both subgroup comparisons; 3.8% Asian, $P=.02$ vs exon 20 insertions and $P<.001$ vs other EGFR mutations). Among patients with insertions in exon 20 of EGFR who had evaluable disease, the greatest activity occurred with platinum-based chemotherapy (mean time to progression, 6.3 months; range, 1.5–19 months; n=17; $P=.001$), compared with 3.1 months on initial exposure to erlotinib or gefitinib (range, 1–4.1 months, n=9). Among 22 patients with exon 20 insertions, median survival for advanced disease was 19 months, which was shorter than the 31-month median survival observed in 166 patients with other EGFR mutations ($P=.002$) and similar to the 21-month median survival of the 561 patients with wild-type EGFR.

Such events were consistent with the immunogenic activity of BMS-936558. Grade 3–5 related AEs occurred in 8% of the NSCLC patients. In patients with NSCLC, fatigue was the most common grade 3/4 toxicity (2% of patients). Grade 1/2 pneumonitis occurred in 6 (2%) patients, including 4 (3%) NSCLC patients. Among the patients with pneumonitis, 3 drug-related deaths occurred (2 patients with NSCLC and 1 with colorectal cancer).

Among the 76 patients with NSCLC who were evaluable for clinical activity, the ORR was 18% (Table 2). There were 14 cases of PR, which occurred at doses of 1 (1 of 18 patients), 3 (6 of 19 patients), and 10 mg/kg (7 of 39 patients), resulting in response rates of 6%, 32%, and 18%, respectively. Two additional NSCLC patients who had received the antibody at a dose of 10 mg/kg were awaiting a confirmatory scan, and thus had unconfirmed PRs.

The anti-PD-1 antibody was active in both squamous and nonsquamous NSCLC histologies. Responses occurred in 6 of the 18 patients with squamous histology (33%) and in 7 of the 56 patients with nonsquamous histology (12.5%). All 14 of the responding patients began treatment more than 24 weeks before the analysis, and 8 of these patients had a response that lasted 24 weeks or longer. Further, 3 patients had a persistent decrease in overall tumor burden in the presence of new lesions, so they were not classified as responders.

BMS-936558 can be administered safely in heavily pretreated NSCLC patients in an outpatient setting. BMS-936558 is well tolerated. The clinical activity of BMS-936558 in patients with previously treated, advanced NSCLC is encouraging and warrants further development of this agent in patients with advanced NSCLC.

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

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

Proteinuria

Grade 3-4 proteinuria ranged from 0.7 to 7.4% in Studies 1, 2, 4 and 7. The overall incidence of proteinuria (all grades) was only adequately assessed in Study 7, in which the incidence was 20%. Median onset of proteinuria was 5.6 months (range 15 days to 37 months) after initiation of Avastin. Median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months). Proteinuria did not resolve in 40% of patients after median follow up of 11.2 months and required permanent discontinuation of Avastin in 30% of the patients who developed proteinuria (Study 7). [See *Warnings and Precautions (5.8).*]

Congestive Heart Failure (CHF)

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

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

Ovarian Failure

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

Metastatic Colorectal Cancer (mCRC)

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

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

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

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

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

AVASTIN® (bevacizumab)

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

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

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

Avastin in Combination with FOLFOX4 in Second-line mCRC

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

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

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

Glioblastoma

All adverse events were collected in 163 patients enrolled in Study 5 who either received Avastin alone or Avastin plus irinotecan. All patients received prior radiotherapy and temozolomide. Avastin was administered at 10 mg/kg every 2 weeks alone or in combination with irinotecan. Avastin was discontinued due to adverse events in 4.8% of patients treated with Avastin alone.

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

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

Metastatic Renal Cell Carcinoma (mRCC)

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

Grade 1–5 adverse events occurring at a higher incidence (≥ 5%) in patients receiving IFN-α plus Avastin compared to the IFN-α plus placebo arm are presented in Table 3.

AVASTIN® (bevacizumab)

Table 3
NCI-CTC Grades 1–5 Adverse Events in Study 7
(Occurring at Higher Incidence [≥ 5%] in IFN-α + Avastin vs. IFN-α + Placebo)

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

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

The following adverse events were reported at a 5-fold greater incidence in the IFN-α plus Avastin arm compared to IFN-α alone and not represented in Table 3: gingival bleeding (13 patients vs. 1 patient); rhinitis (9 vs.0); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux disease (8 vs.1); tinnitus (7 vs. 1); tooth abscess (7 vs.0); mouth ulceration (6 vs. 0); acne (5 vs. 0); deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

6.2 Immunogenicity

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

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

6.3 Postmarketing Experience

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

Body as a Whole: Polyserositis

Cardiovascular: Pulmonary hypertension, RPLS, Mesenteric venous occlusion

Eye disorders (from unapproved intravitreal use for treatment of various ocular disorders): Permanent loss of vision; Endophthalmitis (infectious and sterile); Intraocular inflammation; Retinal detachment; Increased intraocular pressure; Hemorrhage including conjunctival, vitreous hemorrhage or retinal hemorrhage; Vitreous floaters; Ocular hyperemia; Ocular pain or discomfort

Gastrointestinal: Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration

Hemic and lymphatic: Pancytopenia

Hepatobiliary disorders: Gallbladder perforation

Musculoskeletal: Osteonecrosis of the jaw

Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)

Respiratory: Nasal septum perforation, dysphonia

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

7 DRUG INTERACTIONS

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

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

In Study 7, there was no difference in the mean exposure of interferon alfa administered in combination with Avastin when compared to interferon alfa alone.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate or well controlled studies of bevacizumab in pregnant women. While it is not known if bevacizumab crosses the placenta, human IgG is known to cross the placenta Reproduction studies in rabbits treated with approximately 1 to 12 times the recommended human dose of bevacizumab demonstrated teratogenicity, including an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested. Other observed effects included decreases in maternal and fetal body weights and an increased number of fetal resorptions. [See *Nonclinical Toxicology (13.3).*

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

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

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

8.5 Geriatric Use

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

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

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

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

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

8.6 Females of Reproductive Potential

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

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

10 OVERDOSAGE

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

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Clinical Activity of Crizotinib in Advanced Non-Small Cell Lung Cancer (NSCLC) Harboring ROS1 Gene Rearrangement

A new molecular subset of NSCLC is defined by chromosomal rearrangements of the ROS1 receptor tyrosine kinase gene.[1,2] The ROS1 gene encodes a tyrosine kinase receptor, and ROS1 is most closely related to other tyrosine kinases in the insulin receptor superfamily. Rearrangements of ROS1 in cell lines lead to expression of ROS1 fusion kinases and sensitivity to the inhibition of ROS kinase.[3] The primary mechanism that activates ROS1 in lung cancer and other cancers is chromosomal rearrangement, and a number of ROS1 rearrangements can occur in nonsquamous lung cancer. These rearrangements lead to aberrant expression of ROS1 and constitutive activation of its tyrosine kinase.

Rearrangements of ROS1 are rare in nonsquamous NSCLC, occurring in only approximately 1% of patients.[4] Lung cancer patients who have ROS1 rearrangements tend to be younger in age and light or never-smokers, and almost all have adenocarcinoma histology.[2] In general, ROS1 rearrangements are mutually exclusive with other oncogenic drivers.[5]

Crizotinib is a small-molecule tyrosine kinase inhibitor of MET, ALK, and ROS1. Crizotinib was originally developed as a potent tyrosine kinase inhibitor of c-MET, and was subsequently found to inhibit other tyrosine kinases, including ALK and ROS1.[3] More than 600 cell lines were screened for sensitivity to TAE684, a very potent ALK inhibitor.[6] Among the top 10 most sensitive cell lines, 8 had known alterations in ALK. Interestingly, 1 of the sensitive lines was HCC-78, a nonsquamous NSCLC cell line that harbors a ROS1 rearrangement. This cell line screen showed that an ALK inhibitor could have activity in ROS1.

The phase I study of crizotinib included a dose-escalation phase followed by dose expansion. The molecular cohorts were specified, with a molecular expansion cohort included for ROS1 patients. Patients were screened for ROS1 by break-apart fluorescence in situ hybridization (FISH) assay. This study examined the efficacy and safety of crizotinib in patients with advanced, ROS1-rearranged NSCLC.[7] As of April 2012, 15 ROS1-positive patients had received crizotinib, 12 patients were receiving ongoing crizotinib treatment, and 3 patients had discontinued due to disease progression. Data were presented on 14 of the 15 patients who were evaluated for a response (Figure 4). The ROS1-positive patients had a median age of 54 years (range, 31–72 years), and all but 1 were never-smokers. All patients had adenocarcinoma histology. All but 2 of these patients had been previously treated with chemotherapy.

To date, 8 of 12 patients had confirmed CR or PR. Two patients were characterized with SD, and 2 with PD. In 1 of the patients with PD, crizotinib had been discontinued for 6 weeks. He received a scan for unrelated bowel obstruction during the time crizotinib was discontinued. When he went back on crizotinib, his tumor was reduced to approximately 60%. The other patient with PD was initially characterized as ROS1-positive and did have progression on the first scans. When the molecular pathologist revisited his tumor, it was found to have an atypical ROS1 FISH, and he was in fact ROS1-negative.

Typical examples of responses to crizotinib in ROS1-positive patients include a 40-year-old never-smoker who had extensive disease when she started on the trial. She was treated with crizotinib and had a dramatic response after just 4 weeks. Her symptoms also improved greatly, and her disease remained under control for approximately 12 months. Another patient also had extensive disease when he started on the trial; after just 3 months of crizotinib, his disease completely resolved.

The ORR of the 14 ROS1-positive patients treated with crizotinib was 57%. The median duration of treatment was close to 26 weeks. The treatment-related AEs and safety profile of crizotinib were almost identical to what has been seen in ALK-positive patients.

In summary, ROS1 rearrangement does seem to define a new, distinct molecular subset of lung cancer. Crizotinib has marked anti-tumor activity in patients with advanced, ROS1-positive lung cancer. These results are the first to validate ROS1 as a therapeutic target in lung cancer.

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LUX-Lung 3: A Randomized, Open-Label, Phase III Study of Afatinib vs Pemetrexed and Cisplatin as First-Line Treatment For Patients With Advanced Adenocarcinoma of the Lung Harboring EGFR-Activating Mutations (Subgroup Analysis)

Afatinib is an irreversible ErbB family blocker that prevents the homodimerization and heterodimerization of the ErbB family receptor.[1,2] Afatinib has known efficacy in lung adenocarcinoma patients with EGFR mutations.[3] This study was designed to compare afatinib with the now commonly prescribed combination of pemetrexed and cisplatin. Enrollment included 345 patients with stage IIIB or IV advanced lung adenocarcinoma and proven EGFR mutations, as determined in a central screening facility using the TheraScreen polymerase chain reaction (PCR)-based test. Patients were randomized 2:1 to receive afatinib 40 mg daily continuous dosing or chemotherapy with cisplatin and pemetrexed at standard doses every 21 days for up to 6 cycles. The primary endpoint was PFS, as determined by independent review, and secondary endpoints included ORR, time to deterioration in cancer-related symptoms, and safety. A subgroup analysis was planned among patients with common mutations (Del19/L858R). The median PFS for all patients receiving afatinib was 11.1 months, which was more favorable than the 6.9-month PFS for patients receiving chemotherapy with pemetrexed and cisplatin (HR=0.58 [95% CI, 0.43–0.78]; *P*=.0004; Table 3). The ORR was higher with afatinib (56% vs 23%; *P*<.0001). Patients receiving afatinib had a significant delay in the time to deterioration of cancer-related symptoms of cough (HR=0.60; *P*=.0072) and dyspnea (HR=0.68; *P*=.0145) compared with chemotherapy. The most common drug-related AEs seen with afatinib were diarrhea (95%), rash (89%), and paronychia (57%). Nausea (66%), decreased appetite (53%), and vomiting (42%) were the most common AEs related to chemotherapy. Treatment was discontinued due to drug-related AEs in 8% of patients receiving afatinib and in 12% of patients receiving chemotherapy with pemetrexed and cisplatin.

Table 3. LUX-Lung 3: Afatinib Treatment Benefits

Arm	Afatinib	Chemotherapy	*P* Value
Response rate (independent evaluation)	56%	23%	<.0001
Overall PFS (months)	11.1	6.9	.0004
PFS (months) in exons 19 and 21	13.6	6.9	<.0001

PFS=progression-free survival.
Data from Sequist LV et al. LUX-Lung 3: a randomized, open-label, phase III study of afatinib vs pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harboring EGFR-activating mutations (subgroup analysis). Paper presented at: the 2012 Chicago Multidisciplinary Symposium in Thoracic Oncology; September 6-8, 2012; Chicago, IL. Abstract 1.

Subgroup analyses found that 49% (n=170) of patients had the Del19 mutation and 40% (n=138) had L858R. All of the patients with these 2 common mutations benefited from afatinib treatment compared with chemotherapy (HR=0.47; *P*<.0001). Among the 72% of patients who were Asian, afatinib provided a strong benefit compared with chemotherapy (HR=0.44; 95% CI, 0.30–0.63). Asian patients may have had a modestly greater benefit with a slightly longer median PFS and lower HR compared with non-Asian patients.

The distribution of diarrhea, rash, and acneiform rash associated with afatinib treatment was fairly similar across races. However, Asians had higher incidences of paronychia, dry skin, and decreased appetite with afatinib than non-Asians. Among patients treated with chemotherapy, side effects again differed by race, with decreased appetite, vomiting, neutropenia, and leukopenia being more common for Asians than for non-Asians.

Among patients with common EGFR mutations, afatinib offered significant benefit in terms of relieving lung cancer–related symptoms like cough, dyspnea, and pain, with statistical significance for cough and dyspnea. Pain trended in the same direction but did not reach statistical significance.

In summary, LUX-Lung 3 is the largest global prospective trial involving EGFR mutation-positive NSCLC patients to date. It is the first trial to compare a genotype-directed

strategy against one of the most commonly used chemotherapy regimens, cisplatin and pemetrexed. It is also the first clinical trial of this design to be performed in both Asian and non-Asian patients. LUX-Lung 3 met its primary endpoint of PFS by independent radiology review, and it showed a consistent efficacy across all patient subgroups. The efficacy was particularly notable in the largest subset of patients, which included those with the common mutations Del19 and L858R. The safety profile is consistent with previous afatinib trials. Interestingly, toxicity appears to be milder in non-Asian patients. Therefore, afatinib is a first-line treatment option for patients with EGFR-mutated NSCLC.

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Commentary

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For those of us treating patients with advanced non–small cell lung cancer (NSCLC), we have embarked on a new era of personalized therapy dictated by both the unique histology and the molecular fingerprints of the tumor under scrutiny. Our customized strategies have largely replaced the "one size fits all" approach to which we previously defaulted. Recent advances in NSCLC were highlighted in a number of provocative presentations at the 2012 Chicago Multidisciplinary Symposium in Thoracic Oncology.

Predicting Histology

Histology is a critical component in individualizing treatment for patients with NSCLC. The presentation by Robertson[1] and associates addressed the issue of specimen adequacy. Of particular interest was the relatively low overall concordance rate between preoperative and final histologic subtype of 67.2% (80/119 patients with NSCLC). This is concerning, as we are frequently forced to deal with a relatively small specimen at initial diagnosis. Trying to do more with less has been the preferred method, but this observational analysis underscores the hazard of such an approach. It is clear that initial histologic analysis may lead us down the wrong path. Newer treatment strategies are more complex; certain novel therapeutics are restricted to specific histologic or molecular subtypes. This requires more precise classification and performance of molecular testing for actionable biomarkers, such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) translocations. This problem may be exacerbated in advanced NSCLC, where fine needle aspiration is likely to be inadequate in obtaining sufficient tissue for histologic and molecular analysis. A diagnostic strategy for small biopsies lacking differentiation criteria relies on immunohistochemical (IHC) markers that lead to a specific diagnosis in more than 80% of small biopsies. The focus, however, should not be on using an excessive number of IHC stains, but instead on conserving tissue for molecular analysis. Our philosophy has changed in the last 5–7 years; it should take relatively few stains to differentiate adenocarcinoma from squamous cell carcinoma in questionable cases that defy ready histologic identification. TTF-1 is often sufficient to declare adenocarcinoma, and the majority of squamous cell tumors are positive for p63 or p40.

PointBreak

The Eastern Cooperative Oncology Group (ECOG) 4599 trial[2] established a role for bevacizumab in combination with carboplatin and paclitaxel in nonsquamous cell carcinoma of the lung, resulting in a statistically significant response rate (RR), progression-free survival (PFS), and overall survival (OS) advantage when compared to chemotherapy alone. More recently, a phase II trial by Patel and colleagues[3] demonstrated a median OS that exceeded 14 months and an RR of 55% in treatment-naïve, bevacizumab-eligible, advanced NSCLC patients receiving carboplatin, pemetrexed, and bevacizumab. Given the favorable toxicity profile of pemetrexed compared to paclitaxel, many clinicians adopted this regimen in the absence of phase III data. In a plenary session at the 2012 Chicago Multidisciplinary Symposium in Thoracic Oncology, Patel and coworkers provided the first glimpse of results from the landmark PointBreak trial,[4] which compared the ECOG 4599 approach (carboplatin/paclitaxel/bevacizumab) to the strategy piloted by Patel and colleagues (carboplatin/pemetrexed/bevacizumab). Patients without disease progression on the control arm went on to maintenance therapy with bevacizumab alone, while those on the experimental arm received maintenance therapy with combination pemetrexed and bevacizumab. Unfortunately, but unsurprisingly, the pemetrexed-containing regimen offered no therapeutic advantage, with the exception of reduced toxicity. The primary endpoint of improved survival was not met.

A landmark analysis of those patients able to make it onto maintenance therapy suggested a possible advantage for the combination pemetrexed/bevacizumab approach. Adding pemetrexed to bevacizumab was demonstrated to be somewhat better than bevacizumab alone (median OS, 17.7 vs 15.7 months, respectively); however, *P* values and hazard ratios (HRs) were not provided. Similar findings were shown in the AVAPERL (A Study of Avastin [Bevacizumab] With or Without Pemetrexed as Maintenance Therapy After Avastin in First Line in Patients With Non-Squamous Non-

Small Cell Lung Cancer) trial,[5] which had an identical comparison in the maintenance setting. However, to date, there is insufficient evidence to fully recommend the combination of pemetrexed and bevacizumab over bevacizumab alone in the maintenance setting, particularly when we factor in cost. The results of this study reinforce the need to complete the ongoing ECOG 5508 maintenance trial,[6] in which patients who exhibit no disease progression after 4 cycles of combination paclitaxel/carboplatin/bevacizumab are randomized to either continuation maintenance with bevacizumab alone (the standard arm), switch maintenance with pemetrexed, or a hybrid approach employing both bevacizumab and pemetrexed. This trial is slated to enroll 1,236 patients, and anticipates randomization of 864 subjects. OS is the primary endpoint.

Nab-paclitaxel

Unlike paclitaxel injection, nab-paclitaxel does not require the steroid premedication that can be challenging for many patients. In the original report by Socinski and coworkers published in the *Journal of Clinical Oncology*,[7] patients with squamous NSCLC who received nab-paclitaxel appeared to benefit, with a significant improvement in RR (41% vs 24% in the carboplatin/nab-paclitaxel vs carboplatin/solvent-based paclitaxel arms, respectively). There was no difference in PFS or survival between the 2 arms.

However, survival in the nab-paclitaxel arm was significantly longer in the subset of patients aged 70 years or older (median OS, 19.9 vs 10.4 months)[8] and in enrolled patients from North America (12.7 vs 9.8 months).[9] Additionally, patients treated with nab-paclitaxel experienced less neuropathy.[10] Whether these benefits occurred due to the drug or to the schedule remains unclear. This is a major issue that must be addressed in future studies. A more cogent and relevant comparison that would address the issue of schedule versus drug effect might have been weekly therapy with nab-paclitaxel versus weekly therapy with standard cremophor-based paclitaxel at identical or similar doses. There is tremendous interest in performing a formal, prospective, randomized, phase III trial comparing weekly paclitaxel/carboplatin to weekly nab-paclitaxel in elderly patients with NSCLC.

Crizotinib

Riely and coworkers presented a mature update of a phase II trial that evaluated crizotinib in patients with advanced, ALK-positive NSCLC.[11] Of the 261 patients enrolled, 94% had adenocarcinoma, 67% were never smokers, 53% had received 3 or more prior regimens, and 17% of patients had performance scores of 2 or 3. The 60% overall response rate (ORR) matched that observed in the phase I study. The PFS was approximately 8 months at the time of presentation, and median survival has not been reached. Overall, crizotinib demonstrated a very reasonable safety profile. Based on the Lung Cancer Symptom Scale, crizotinib produced improvements in fatigue, cough, dyspnea, and chest pain, as well as quality of life.

A phase III trial comparing crizotinib to combination pemetrexed and cisplatin in treatment-naïve, ALK-positive, NSCLC patients is ongoing.[12] There is also a separate phase III trial in the second-line setting comparing crizotinib to standard chemotherapy with either docetaxel or pemetrexed.[13] PFS is the primary endpoint. A press release of the results documented a significant improvement in PFS for crizotinib.[14]

Afatinib

Sequist and associates presented updates from the LUX-Lung 3 trial, which compared afatinib to cisplatin and pemetrexed in the first-line setting of treatment-naïve patients with advanced adenocarcinoma of the lung harboring EGFR mutations.[15] Afatinib demonstrated superiority with respect to RR and PFS, and these benefits were even more pronounced in patients whose tumors harbored activating mutations in exons 19 and 21. A number of other trials have examined erlotinib and gefitinib in the identical therapeutic setting. These studies have consistently shown a statistically significant and clinically meaningful benefit with regard to RR and PFS. However, the afatinib trial is distinguished by a variety of factors: 1) it is the largest trial in the first-line, EGFR-mutant setting; 2) it is the first to use a second-generation irreversible EGFR tyrosine kinase inhibitor (TKI); 3) it employs a state-of-the-art comparator (pemetrexed and cisplatin); 4) it integrates quality of life evaluation into outcome analysis; and 5) it is a global registration trial. It was a rather bold move to include resistance mutations in this study, as this might have sabotaged the entire trial. However, despite such inclusion, the data were still positive. Afatinib is now available in the United States through expanded access programs. I presume it will be formally approved by the US Food and Drug Administration in the next several months. Whether it displaces erlotinib in use remains to be seen.

Dacomitinib

A randomized phase II trial recently reported by Ramalingam and colleagues in the *Journal of Clinical Oncology*[16] suggests that dacomitinib may have greater activity than erlotinib in advanced NSCLC. The study compared dacomitinib with erlotinib as second-line therapy in an unselected population. Median PFS favored dacomitinib (2.86 vs 1.91 months), with an HR of 0.66. There was a similar prevalence of EGFR mutations (16%) and KRAS mutations (16.4%) between groups. However, there was an imbalance in

the number of EGFR-mutant patients receiving dacomitinib (20.2%) versus those receiving erlotinib (11.7%). Ramalingam and coworkers presented efficacy analyses in the subgroup of patients with EGFR mutations.[17]

Roughly 1 out of every 5 patients had unknown EGFR mutation status. The standard formula used for estimating sample size assumed a homogeneous population. However, the accuracy of such an estimate is questionable when the population is a heterogeneous mix of patients with and without EGFR mutations. This is especially true when the impact of an EGFR TKI is significantly different between the 2 groups. Even slight differences must be interpreted with caution due to the lack of certainty of equality in the incidence of EGFR mutation between the 2 study arms. Nevertheless, it was found that the KRAS wild-type subgroup had a greater benefit from dacomitinib. The small sample size precludes definitive conclusions regarding whether mutations in exon 19 are predictive of treatment effects. Toxicities were more common in the dacomitinib group. Nonetheless, dacomitinib produced clinically meaningful improvements in disease symptoms, including cough, dyspnea, and chest pain.

Anti-PD–1

Historically, immunotherapies have not offered any significant improvements in therapeutic outcome in advanced NSCLC. Brahmer and associates presented the preliminary results of an ongoing phase I/II trial evaluating the activity and safety of BMS-936558 in patients with advanced NSCLC.[18] BMS-936558 is a fully human IgG4 antibody that blocks the programmed death-1 (PD-1) protein, overcoming immune resistance and mediating tumor regression. This was part of a much larger phase I/II trial involving multiple cancer types.[19] The threshold dose for therapeutic activity was 3 mg/kg intravenously every 2 weeks. There was an ORR of 18%, which rivals that observed with conventional cytotoxics. Responses, when they occurred, were relatively durable. Preferential activity, it seems, was observed in squamous cell carcinoma. In the 13 patients with squamous cell carcinoma receiving either 3 or 10 mg/kg, the RR was 46%. It remains unclear whether this advantage in squamous cell carcinoma is real or serendipitous. At present, there is no known reliable marker for activity. However, it has been suggested that the absence of programmed death ligand 1 expression may correlate with an absence of clinical benefit. Accordingly, phase II trials involving immunologic and molecular-marker correlates are under way,[20,21] and phase III studies of anti-PD–1 antibodies for the treatment of NSCLC, melanoma, and renal cell carcinoma are being developed.

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AVASTIN® (bevacizumab)

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

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

Gastrointestinal Perforations

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

Surgery and Wound Healing Complications

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

Hemorrhage

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

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer (mCRC)

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

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

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

1.3 Glioblastoma

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

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

1.4 Metastatic Renal Cell Carcinoma (mRCC)

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Perforations

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

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

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

5.2 Surgery and Wound Healing Complications

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

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

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

5.3 Hemorrhage

Avastin can result in two distinct patterns of bleeding: minor hemorrhage, most commonly Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin compared to patients receiving only chemotherapy. Across indications, the incidence of Grade ≥ 3 hemorrhagic events among patients receiving Avastin ranged from 1.2 to 4.6%. [See *Adverse Reactions (6.1)*.]

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

In clinical studies in non–small cell lung cancer where patients with CNS metastases who completed radiation and surgery more than 4 weeks prior to the start of Avastin

were evaluated with serial CNS imaging, symptomatic Grade 2 CNS hemorrhage was documented in one of 83 Avastin-treated patients (rate 1.2%, 95% CI 0.06%–5.93%).

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

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

5.4 Non-Gastrointestinal Fistula Formation

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

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

5.5 Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a higher incidence in patients receiving Avastin compared to those in the control arm. Across indications, the incidence of Grade ≥ 3 ATE in the Avastin containing arms was 2.6% compared to 0.8% in the control arms. Among patients receiving Avastin in combination with chemotherapy, the risk of developing ATE during therapy was increased in patients with a history of arterial thromboembolism, or age greater than 65 years. [See *Use in Specific Populations (8.5).*]

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

5.6 Hypertension

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

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

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

5.7 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

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

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

5.8 Proteinuria

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

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

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

5.9 Infusion Reactions

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

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

5.10 Ovarian Failure

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

6 ADVERSE REACTIONS

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

- Gastrointestinal Perforations [See *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.1).*]
- Surgery and Wound Healing Complications [See *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.2).*]
- Hemorrhage [See *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.3).*]
- Non-Gastrointestinal Fistula Formation [See *Dosage and Administration (2.4), Warnings and Precautions (5.4).*]
- Arterial Thromboembolic Events [See *Dosage and Administration (2.4), Warnings and Precautions (5.5).*]
- Hypertensive Crisis [*See Dosage and Administration (2.4), Warnings and Precautions (5.6).*]
- Reversible Posterior Leukoencephalopathy Syndrome [See *Dosage and Administration (2.4), Warnings and Precautions (5.7).*]
- Proteinuria [See *Dosage and Administration (2.4), Warnings and Precautions (5.8).*]
- Ovarian Failure [See *Warnings and Precautions (5.10), Use in Specific Populations (8.6).*]

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

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

6.1 Clinical Trial Experience

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

The data below reflect exposure to Avastin in 4198 patients with CRC, non-squamous NSCLC, glioblastoma, or mRCC trials including controlled (Studies 1, 2, 4, and 7) or uncontrolled, single arm (Study 5) treated at the recommended dose and schedule for a median of 8 to 23 doses of Avastin. [See *Clinical Studies (14).*] The population was aged 18-88 years (median 60 years), 43.6% male and 83.8% white. The population included 1783 first- and second-line mCRC patients who received a median of 10 doses of Avastin, 480 first-line metastatic NSCLC patients who received a median of 8 doses of Avastin, 163 glioblastoma patients who received a median of 9 doses of Avastin, and 337 mRCC patients who received a median of 16 doses of Avastin. These data also reflect exposure to Avastin in 363 patients with metastatic breast cancer (MBC) who received a median of 9.5 doses of Avastin, 669 female adjuvant CRC patients who received a median of 23 doses of Avastin and exposure to Avastin in 403 previously untreated patients with diffuse large B-cell lymphoma (DLBCL) who received a median of 8 doses of Avastin. Avastin is not approved for use in MBC, adjuvant CRC, or DLBCL.

Surgery and Wound Healing Complications

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

In Study 5, events of post-operative wound healing complications (craniotomy site wound dehiscence and cerebrospinal fluid leak) occurred in patients with previously treated glioblastoma: 3/84 patients in the Avastin alone arm and 1/79 patients in the Avastin plus irinotecan arm. [See *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.2).*]

Hemorrhage

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

Venous Thromboembolic Events

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

The risk of developing a second thromboembolic event while on Avastin and oral anticoagulants was evaluated in two randomized studies. In Study 1, 53 patients (14%) on the bolus-IFL plus Avastin arm and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose warfarin following a venous thromboembolic event (VTE). Among these patients, an additional thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus Avastin and 3% (1/30) of patients receiving bolus-IFL alone.

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

Neutropenia and Infection

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

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

Proteinuria

Grade 3-4 proteinuria ranged from 0.7 to 7.4% in Studies 1, 2, 4 and 7. The overall incidence of proteinuria (all grades) was only adequately assessed in Study 7, in which the incidence was 20%. Median onset of proteinuria was 5.6 months (range 15 days to 37 months) after initiation of Avastin. Median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months). Proteinuria did not resolve in 40% of patients after median follow up of 11.2 months and required permanent discontinuation of Avastin in 30% of the patients who developed proteinuria (Study 7). [See *Warnings and Precautions (5.8).*]

Congestive Heart Failure (CHF)

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

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

Ovarian Failure

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

Metastatic Colorectal Cancer (mCRC)

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

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

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

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

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

Grade 1–4 adverse events which occurred at a higher incidence (≥ 5%) in patients receiving bolus-IFL plus Avastin as compared to the bolus-IFL plus placebo arm are presented in Table 2. Grade 1–4 adverse events were collected

for the first approximately 100 patients in each of the three treatment arms who were enrolled until enrollment in Arm 3 (5-FU/LV + Avastin) was discontinued.

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

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

Avastin in Combination with FOLFOX4 in Second-line mCRC

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

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

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

Glioblastoma

All adverse events were collected in 163 patients enrolled in Study 5 who either received Avastin alone or Avastin plus irinotecan. All patients received prior radiotherapy and temozolomide. Avastin was administered at 10 mg/kg every 2 weeks alone or in combination with irinotecan. Avastin was discontinued due to adverse events in 4.8% of patients treated with Avastin alone.

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

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

Metastatic Renal Cell Carcinoma (mRCC)

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

Grade 1–5 adverse events occurring at a higher incidence (≥ 5%) in patients receiving IFN-α plus Avastin compared to the IFN-α plus placebo arm are presented in Table 3.

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Table 3
NCI-CTC Grades 1–5 Adverse Events in Study 7
(Occurring at Higher Incidence [≥ 5%] in IFN-α + Avastin vs. IFN-α + Placebo)

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

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

The following adverse events were reported at a 5-fold greater incidence in the IFN-α plus Avastin arm compared to IFN-α alone and not represented in Table 3: gingival bleeding (13 patients vs. 1 patient); rhinitis (9 vs.0); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux disease (8 vs.1); tinnitus (7 vs. 1); tooth abscess (7 vs.0); mouth ulceration (6 vs. 0); acne (5 vs. 0); deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

6.2 Immunogenicity

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

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

6.3 Postmarketing Experience

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

Body as a Whole: Polyserositis

Cardiovascular: Pulmonary hypertension, RPLS, Mesenteric venous occlusion

Eye disorders (from unapproved intravitreal use for treatment of various ocular disorders): Permanent loss of vision; Endophthalmitis (infectious and sterile); Intraocular inflammation; Retinal detachment; Increased intraocular pressure; Hemorrhage including conjunctival, vitreous hemorrhage or retinal hemorrhage; Vitreous floaters; Ocular hyperemia; Ocular pain or discomfort

Gastrointestinal: Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration

Hemic and lymphatic: Pancytopenia

Hepatobiliary disorders: Gallbladder perforation

Musculoskeletal: Osteonecrosis of the jaw

Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)

Respiratory: Nasal septum perforation, dysphonia

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

7 DRUG INTERACTIONS

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

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

In Study 7, there was no difference in the mean exposure of interferon alfa administered in combination with Avastin when compared to interferon alfa alone.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate or well controlled studies of bevacizumab in pregnant women. While it is not known if bevacizumab crosses the placenta, human IgG is known to cross the placenta Reproduction studies in rabbits treated with approximately 1 to 12 times the recommended human dose of bevacizumab demonstrated teratogenicity, including an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested. Other observed effects included decreases in maternal and fetal body weights and an increased number of fetal resorptions. [See *Nonclinical Toxicology (13.3)*.]

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

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

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

8.5 Geriatric Use

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

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

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

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

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

8.6 Females of Reproductive Potential

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

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

10 OVERDOSAGE

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

Genentech
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Avastin® (bevacizumab)

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

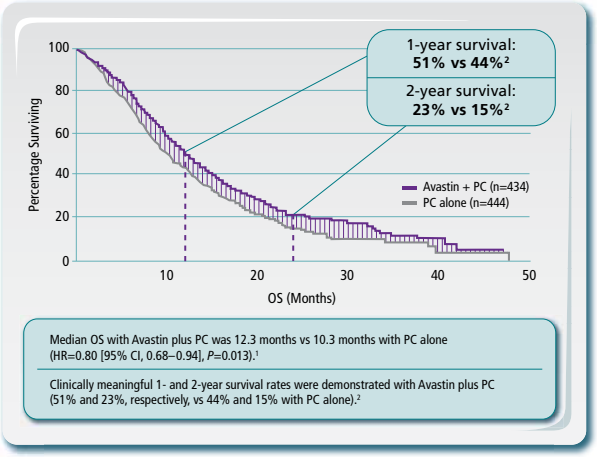
To confront the threat of angiogenesis
in first-line metastatic non-squamous NSCLC…

Think Avastin

Because survival matters most

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

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



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

Indication

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

Boxed WARNINGS

- **Gastrointestinal (GI) perforation**
  - — Serious and sometimes fatal GI perforation occurs at a higher incidence in Avastin-treated patients compared to controls
  - — The incidences of GI perforation ranged from 0.3% to 2.4% across clinical studies
  - — Discontinue Avastin in patients with GI perforation
- **Surgery and wound healing complications**
  - — The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients
  - — Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined
  - — Discontinue Avastin at least 28 days prior to elective surgery and in patients with wound healing complications requiring medical intervention
- **Hemorrhage**
  - — Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin. Across indications, the incidence of grade ≥3 hemorrhagic events among patients receiving Avastin ranged from 1.2% to 4.6%
  - — Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis (≥1/2 tsp of red blood)
  - — Discontinue Avastin in patients with serious hemorrhage (ie, requiring medical intervention)

Additional serious adverse events

- Additional serious and sometimes fatal adverse events with increased incidence in the Avastin-treated arm vs control included
  - — Non-GI fistula formation (≤0.3%)
  - — Arterial thromboembolic events (grade ≥3, 2.4%)
  - — Proteinuria including nephrotic syndrome (<1%)
- Additional serious adverse events with increased incidence in the Avastin-treated arm vs control included
  - — Hypertension (grade 3–4, 5%–18%)
  - — Reversible posterior leukoencephalopathy syndrome (RPLS) (<0.1%)
- Infusion reactions with the first dose of Avastin were uncommon (<3%), and severe reactions occurred in 0.2% of patients
- Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin

Most common adverse events

- Most common adverse reactions observed in Avastin patients at a rate >10% and at least twice the control arm rate were
  - — Epistaxis
  - — Headache
  - — Hypertension
  - — Rhinitis
  - — Proteinuria
  - — Taste alteration
  - — Dry skin
  - — Rectal hemorrhage
  - — Lacrimation disorder
  - — Back pain
  - — Exfoliative dermatitis
- Across all studies, Avastin was discontinued in 8.4% to 21% of patients because of adverse reactions

Pregnancy warning

- Avastin may impair fertility
- Based on animal data, Avastin may cause fetal harm
- Advise patients of the potential risk to the fetus during and following Avastin and the need to continue adequate contraception for at least 6 months following the last dose of Avastin
- For nursing mothers, discontinue nursing or Avastin, taking into account the importance of Avastin to the mother
- Grade 3–5 (nonhematologic) and grade 4–5 (hematologic) adverse events in Study E4599 occurring at a ≥2% higher incidence in Avastin-treated patients vs controls were neutropenia (27% vs 17%), fatigue (16% vs 13%), hypertension (8% vs 0.7%), infection without neutropenia (7% vs 3%), venous thrombus/embolism (5% vs 3%), febrile neutropenia (5% vs 2%), pneumonitis/pulmonary infiltrates (5% vs 3%), infection with grade 3 or 4 neutropenia (4% vs 2%), hyponatremia (4% vs 1%), headache (3% vs 1%), and proteinuria (3% vs 0%)

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

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

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