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Recent Advances in Taxanes for the First-Line Treatment of Advanced Non–Small Cell Lung Cancer

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Abstract: Treatments for non–small cell lung cancer (NSCLC) are based on the broad categories of squamous or non-squamous histology. Frontline treatment options include pemetrexed and cisplatin, pemetrexed and a taxane, gemcitabine with cisplatin, and the addition of bevacizumab to a taxane and carboplatin. Pemetrexed is used for maintenance therapy for non-squamous NSCLC, whereas patients with squamous NSCLC lack easy options for maintenance therapy. nab®-Paclitaxel overcomes the solubility and toxicity issues of solvent-based paclitaxel, and the albumin in nab-paclitaxel improves the concentration of the drug in the tumor. A recent phase III trial in NSCLC compared nab-paclitaxel with carboplatin versus solvent-based paclitaxel with carboplatin, and found improved overall response rates (ORRs) in the nab-paclitaxel arm (33% vs 25%; $P=.005$). In a subset analysis, NSCLC patients with squamous histology had a higher ORR (41%) with nab-paclitaxel than with solvent-based paclitaxel (24%; $P<.001$). Another subset analysis found that patients ages 70 years and older had improved overall survival (median 19.9 months) with nab-paclitaxel compared with solvent-based paclitaxel (median 10.4 months; $P=.009$). Patients in the nab-paclitaxel arm had less neuropathy, less hearing loss, and fewer interruptions in daily living than patients in the solvent-based paclitaxel arm.

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Histology Influences First-Line Decision Making

In contrast to 5 years ago, patients with non–small cell lung cancer (NSCLC) are now being selected based on histology and biomarkers. In the frontline setting, histology has 2 broad categories: squamous and non-squamous NSCLC. There are several therapies for non-squamous NSCLC. The first option is pemetrexed. The combination of cisplatin and pemetrexed was shown to be superior to cisplatin and gemcitabine in non-squamous NSCLC in a trial by Scagliotti and colleagues.[1] Overall survival (OS) was statistically superior with the cisplatin/pemetrexed regimen versus the cisplatin/gemcitabine regimen in 847 patients with adenocarcinoma (12.6 vs 10.9 months, respectively) and 153 patients with large-cell carcinoma (10.4 vs 6.7 months, respectively). In contrast, in the 473 patients with squamous cell histology, the cisplatin/gemcitabine regimen showed a significant improvement in survival as compared with cisplatin/pemetrexed (10.8 vs 9.4 months, respectively). This prospective phase III study was the first to show survival differences according to histologic type in NSCLC. Among all patients, OS in the cisplatin/pemetrexed arm was noninferior to that in the cisplatin/gemcitabine arm (median survival, 10.3 vs 10.3 months, respectively; hazard ratio [HR], 0.94; 95% confidence interval [CI], 0.84–1.05). Patients in the cisplatin/pemetrexed arm had significantly lower rates of grade 3/4 neutropenia, anemia, and thrombocytopenia ($P \leq .001$); febrile neutropenia ($P = .002$); and alopecia ($P < .001$). Cisplatin/pemetrexed was associated with higher rates of grade 3/4 nausea ($P = .004$). The authors concluded that in advanced NSCLC, cisplatin/pemetrexed provided similar efficacy with better tolerability and more convenient administration than cisplatin/gemcitabine. These results support the argument that a pemetrexed-based regimen should be an option—since pemetrexed appears superior to gemcitabine—and led to the approval of pemetrexed in the frontline setting for patients with non-squamous NSCLC. However, pemetrexed has not been shown to be superior to a taxane in the frontline setting.

In the Eastern Cooperative Oncology Group (ECOG) phase III trial E4599, the addition of bevacizumab to carboplatin-paclitaxel improved OS and progression-free survival (PFS) compared with carboplatin-paclitaxel alone.[2] Among patients who received bevacizumab plus carboplatin-paclitaxel, the median survival was 12.3 months, as compared with 10.3 months in the chemotherapy-alone group (HR for death, 0.79; $P = .003$). PFS was 6.2 months in the bevacizumab arm and 4.5 months in the chemotherapy-only arm (HR for disease progression, 0.66; $P < .001$), with response rates of 35% and 15% ($P < .001$). Rates of clinically significant bleeding were higher in the patients who received bevacizumab (4.4% vs 0.7%, respectively ($P < .001$). Among 15 treatment-related deaths in the chemotherapy-plus-bevacizumab group, 5 were from pulmonary hemorrhage.

Notably, some studies have raised concerns about the lack of efficacy and safety of bevacizumab in elderly patients.[3,4] However, in the absence of obvious contraindications, bevacizumab with a taxane is certainly an appropriate combination for this group of patients. A recent report found that patients with non-squamous NSCLC experienced better overall response rates (ORR) and more toxicities when treated with platinum-based doublets combined with bevacizumab than when treated with platinum-based doublets combined with pemetrexed.[5] ORR was 60.0% in the bevacizumab group and 35.7% in the pemetrexed group ($P = .04$). Median survival was also higher in the bevacizumab group compared to the pemetrexed group (26.4 vs 16.4 months; $P = .009$). Median PFS was not significantly different between the groups (10.5 vs 7.7 months; $P = .06$). Patients receiving bevacizumab were more likely to experience grade 3/4 neutropenia (27.5% vs 9.5%; $P = .03$) and neuropathy (17.5% vs 0%; $P = .005$).

Maintenance Therapy for Non-Squamous Histology

For non-squamous NSCLC in the absence of disease progression, the duration for doublet therapy is approximately 4 cycles. Afterward, maintenance therapy is given until disease progression. The selection of patients for maintenance treatment is an important consideration in non-squamous NSCLC. Maintenance therapy appears to improve OS and outcomes, particularly with pemetrexed maintenance in non-squamous NSCLC.[6,7] Whether or not a patient received pemetrexed in the frontline setting, maintenance therapy with pemetrexed is reasonable and improves OS in patients who have had either partial response or stable disease after 4 cycles of induction therapy. In a trial presented at the 20th Chicago Multidisciplinary Symposium in Thoracic Oncology in September 2012, pemetrexed improved PFS but not OS compared with the taxane paclitaxel.[8] This randomized, open-label, phase III superiority study compared a regimen of pemetrexed plus carboplatin plus bevacizumab followed by maintenance pemetrexed plus bevacizumab versus paclitaxel plus carboplatin plus bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV non-squamous NSCLC. PFS in the pemetrexed arm was significantly higher than in the paclitaxel arm (6.0 vs 5.6 months; HR, 0.83; *P*=.012). There was no significant difference in median OS (12.6 vs 13.4 months; HR, 1.00; *P*=.949). Treatment with pemetrexed was associated with significantly more study drug–related grade 3/4 anemia (14.5% vs 2.7%), thrombocytopenia (23.3% vs 5.6%), and fatigue (10.9% vs 5.0%) than paclitaxel. Paclitaxel was associated with more grade 3/4 neutropenia (40.6% vs 25.8%), febrile neutropenia (4.1% vs 1.4%), and sensory neuropathy (4.1% vs 0%), as well as complete alopecia (grade 2; 21.4% vs 1.1%), than pemetrexed.

No agent other than pemetrexed has been shown to improve OS in NSCLC. Across all histologic subtypes, docetaxel improves PFS but not OS.[9] Erlotinib has some effect on PFS as a maintenance treatment, and it is FDA-approved for use in this setting.[10] Generally, pemetrexed is being used in the non-squamous NSCLC setting.[11]

Maintenance Therapy for Squamous Histology

For squamous cell NSCLC, platinum-based doublets, such as taxanes, are used in the frontline setting for 4 cycles. For squamous cell lung cancer, the use of bevacizumab should be avoided, especially if the patient has a tumor in the lung. Whether to use maintenance therapy is not an easy decision in patients with squamous cell lung cancer. Pemetrexed is probably not active in this group of patients.[12] Docetaxel improves PFS but not OS.[9] Likewise, erlotinib improves PFS but not OS across histologic subtypes.[10] Thus, in patients with squamous cell lung cancer, treatment stops after 4 cycles of doublet therapy. Taxanes, including paclitaxel and docetaxel, are commonly used in this group of patients.

The outcomes, rates of recurrent disease, and rates of adverse events (AEs) are approximately the same for the various maintenance therapy options. The toxicities are unique, with neuropathy occurring with taxanes, fatigue with pemetrexed, myelosuppression with carboplatin, and both neuropathy and renal toxicity with cisplatin.

EGFR Status and Treatment

The epidermal growth factor receptor (EGFR) mutation status is checked for non-squamous NSCLC, and these patients are started on pemetrexed and carboplatin. Patients with wild-type EGFR who do well after 4 cycles of therapy are continued on pemetrexed maintenance. Patients with an EGFR mutation have 2 options: they can receive pemetrexed until disease progression and then receive erlotinib, the EGFR tyrosine kinase inhibitor, or they can switch from pemetrexed to erlotinib in the maintenance setting. Chemotherapy is usually not stopped if the patient is doing well, even if the patient is known to have an EGFR mutant tumor during cycle 1. If a patient is known to have an EGFR mutation from the beginning of treatment, erlotinib will be given as a single agent and continued until disease progression. As the patient's disease progresses, pemetrexed and carboplatin are started, with erlotinib continuing the whole time.

Additional Treatment Selection Criteria

Bevacizumab is used in certain patients who are younger than 65 or 70 years and who have no contraindications. A recent phase II trial of a regimen of pemetrexed, carboplatin, and bevacizumab found it to be feasible and tolerable,[13] although it may not be superior to a taxane.

In the near future, tumors will be genotyped, which will provide the basis for selecting therapy. In general, EGFR tyrosine kinase inhibitors should not be combined with chemotherapy in the frontline setting. Sorafenib or sunitinib should not be used in NSCLC, except in the context of a clinical trial.

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Emerging Taxanes in First-Line Treatment of Non–Small Cell Lung Cancer

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The taxanes paclitaxel and docetaxel are established as standards of care in the first-line setting of advanced-disease NSCLC. However, these agents have known toxicity and issues with solubility. They are not water soluble, so they must be dissolved in certain solutions for administration. For example, paclitaxel is typically dissolved in Cremophor and alcohol, which may contribute to the toxicity profile for solvent-based paclitaxel. Infusion reactions range from intolerability—if the infusion is started too rapidly, patients may develop grade 1 and 2 reactions—to severe hypersensitivity reactions in sensitive patients.

The development of the 130 nm albumin-bound formulation of paclitaxel (also known as nab®-paclitaxel [Abraxane®, Celgene, Summit, NJ]) is an emerging and successful strategy. Years ago, several approaches to alter the formulation of paclitaxel were pursued in attempts to simplify administration by making paclitaxel water-soluble. Polyglutamated paclitaxel, one such approach, was tested in phase III trials that compared this compound to standard therapies. Unfortunately, the results of these phase III trials were negative, halting the development of polyglutamated paclitaxel.[1,2]

A successful strategy has been realized with nab-paclitaxel, in which paclitaxel is bound to albumin. nab-Paclitaxel has been available for breast cancer therapy for several years now, based on randomized clinical trial data showing an advantage over other taxanes.[3-7]

Table 1. Studies of nab-Paclitaxel in NSCLC

Single-Agent Studies			
Author	**Phase**	**N**	**Regimen**
Green et al[16] (2006)	II	43	Nab-paclitaxel 260 mg/m^2 q3w
Rizvi et al[17] (2008)	I/II	40	Nab-paclitaxel 100/125/150 mg/m^2 days 1, 8, 15, q4w
Combination Studies			
Author	**Phase**	**N**	**Regimens**
Allerton et al[24] (2006)	II	50	Nab-paclitaxel 100 mg/m^2 days 1, 8, 15 Carboplatin AUC 6 94 weeks
Reynolds et al[18] (2009)	II	50	Nab-paclitaxel 300 mg/m^2 + carboplatin + bevacizumab q3w
Socinski[22] (2010)	II	175	7 cohorts
Socinksi[23] (2012)	III	1,052	Nab-paclitaxel 100 mg/m^2 qw (no premedication) + carboplatin Paclitaxel 200 mg/m^2 q3w (+ premedication) + carboplatin

AUC=area under the curve; NSCLC=non–small cell lung cancer.

Table 2. nab-Paclitaxel NSCLC First-Line Trial Comparison

Trial/Author	**Green et al[16]**	**Rizvi et al[17]**	**Allerton et al[24]**	**Reynolds et al[18]**
Nab-paclitaxel	260 mg/m^2 q3w	100–150 mg/m^2 q3/4w Then 125 mg/m^2 q3/4w	100 mg/m^2 q3/4w	300 mg/m^2 q3w
Partner drug	–	–	Carboplatin AUC 6	Carboplatin AUC 6 Bevacizumab 15 mg/kg
N	43	40	50	50
ORR (%)	16	30	50	31.3
PFS (median, months)	NR	NR	NR	9.8
OS (median, months)	11	11	NR	16.8
Neutropenia* (%)	9	20	44	54
Thrombocytopenia (%)	0	NR	25	10
Anemia (%)	0	8	9	NR
Peripheral neuropathy (%)	5	15	0	4
Fatigue (%)	7	18	NR	17

*All adverse events are grade 3/4.

AUC=area under the curve; NSCLC=non–small cell lung cancer; ORR=overall response rate; OS=overall survival; PFS=progression-free survival.

nab-Paclitaxel Mechanisms of Action

Compared with solvent-based paclitaxel, nab-technology uses albumin to deliver paclitaxel to tumors, resulting in 10-fold higher mean C_{max} of free paclitaxel,[8] delivery of 33% higher drug concentration to tumors in preclinical xenograft models,[9] and enhanced transport across endothelial cell monolayers.[9] The use of albumin dispenses the need for solvents, which have been shown to limit drug bioavailability by entrapping drug in micelles.[10-12]

Albumin has an interesting biology in regard to tumors. Endothelial cells have the glycoprotein 60 (gp60) receptor, which binds albumin and brings it into the cytoplasm. In the cytoplasm, vesicles are made to transport albumin across the endothelial cells and into the tumor microenvironment. That transcytotic pathway involves caveolin-1.[9] Another mechanism used by albumin to reach tumors is enhanced permeation and retention (EPR).[13,14] An interesting aspect of the biology of albumin is that tumors secrete a protein called SPARC (secreted protein acidic and rich in cysteine) which is an albumin-binding agent.[15] Consequently, tumors seem to have a mechanism to sequester albumin. The correlation between SPARC and nab-paclitaxel remains to be determined at this point. In preclinical animal models, nab-paclitaxel exhibited increased endothelial cell binding as compared with solvent-based paclitaxel, which led to improved concentration of the drug at the level of the tumor and persistence of the drug in the tumor.[9]

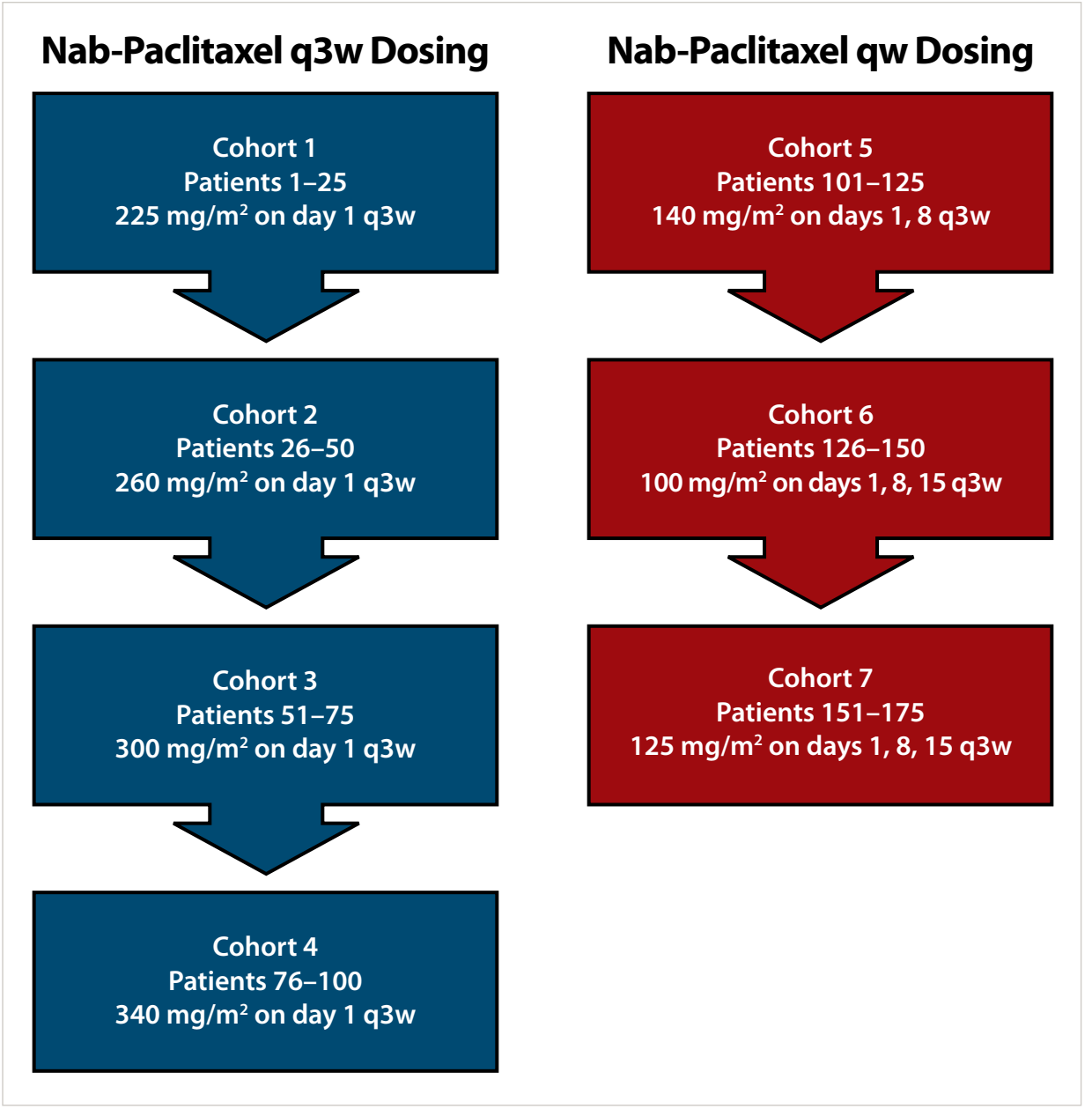

Figure 1. Dose-finding phase II nab-paclitaxel plus carboplatin every 3 weeks and every week dosing cohorts. AUC=area under the curve; NSCLC=non–small cell lung cancer. Adapted with permission from Socinski MA et al. A dose finding study of weekly and every-3-week nab-Paclitaxel followed by carboplatin as first-line therapy in patients with advanced non-small cell lung cancer. *J Thorac Oncol.* 2010;5(6):852-861.[22]

nab-Paclitaxel in NSCLC

Studies of nab-paclitaxel in NSCLC began several years ago with 2 single-agent trials.[16,17] The trials had different schedules, but both showed single-agent activity that was much like the parent compound paclitaxel. Subsequent trials evaluated the combination of nab-paclitaxel with carboplatin (Tables 1 and 2).[18,19] Previous trials that looked at solvent-based paclitaxel administered either every 3 weeks or weekly did not show any difference in efficacy outcomes for either schedule.[20,21] A large phase II dose-finding study examined various doses and schedules in 4 successive cohorts of 25 patients treated initially with nab-paclitaxel every 3 weeks.[22] This dose-finding trial was subsequently expanded with an additional 3 cohorts that explored the use of weekly nab-paclitaxel with carboplatin

Table 3. Dose-Finding Phase II nab-Paclitaxel Plus Carboplatin Clinical Response

	Dose q3w				Dose qw		
Dosing Cohort	225 mg/m^2	260 mg/m^2	300 mg/m^2	340 mg/m^2	140 mg/m^2	100 mg/m^2	125 mg/m^2
Stage IV (%)	60	68	84	88	84	84	72
ORR (%)	40	24	24	32	56	48	36
SD ≥16 weeks (%)	20	32	12	0	8	8	12
ORR + SD (%)	60	56	36	32	64	56	48
Median PFS (months)	6.9	6.5	5.3	4.8	5.6	6.2	6.4
Median OS (months)	10.7	12.2	8.3	14.6	12.0	11.3	15.0

ORR=overall response rate; OS=overall survival; PFS=progression-free survival; SD=stable disease.

Adapted from Socinski MA et al. *J Thorac Oncol.* 2010;5:852-861.[22]

Table 4. Most Common Grade 4 Adverse Events Associated With nab-Paclitaxel at Various Doses

	Dose q3w				Dose qw		
Dosing Cohort	225 mg/m^2	260 mg/m^2	300 mg/m^2	340 mg/m^2	140 mg/m^2	100 mg/m^2	125 mg/m^2
Grade 4 neutropenia (%)	32	24	12	20	44	28	32
Grade 4 thrombocytopenia (%)	12	4	8	4	12	4	16
Peripheral neuropathy (%)*							
Grade 1 (%)	8	40	36	24	28	32	20
Grade 2 (%)	40	20	20	16	16	4	16
Grade 3 (%)	12	16	24	48	8	8	12
Grade 4 (%)	–	–	–	–	–	–	–

*Among patients in the 100-mg/m^2 arm, peripheral neuropathy improved from grade 3 to grade 2 or lower in 15 days.

Adapted from Socinski MA et al. *J Thorac Oncol.* 2010;5:852-861.[22]

every 3 weeks (Figure 1).[22] Among the 7 total cohorts, all patients received carboplatin at an AUC of 6 every 3 weeks. The trial was not randomized, as the objective was to determine the most efficacious and best-tolerated regimen in terms of survival outcomes, response rates, and toxicity profiles. Based on the dose-finding study results, weekly administration of nab-paclitaxel with carboplatin offered the best efficacy and the best toxicity (Tables 3 and 4). The schedule that moved forward was carboplatin AUC of 6 every 3 weeks and nab-paclitaxel at 100 mg/m^2 on days 1, 8, and 15 based on the best clinical benefit-risk ratio. This regimen has no treatment break.

Based on the results of the phase II dose-finding study, a phase III trial was undertaken to compare the efficacy and safety of weekly nab-paclitaxel plus carboplatin every 3 weeks with solvent-based paclitaxel plus carboplatin every 3 weeks.[23] In this global, randomized trial, the primary endpoint was ORR.[23] Because this trial was testing a new formulation of an existing drug, response rate could be used as the endpoint according to regulations from the US Food and Drug Administration (FDA). Secondary endpoints were PFS and OS. A total of 1,052 untreated patients with stage IIIB to IV NSCLC received carboplatin at an AUC of 6 every 3 weeks. Patients were then randomly assigned to receive nab-paclitaxel at 100 mg/m^2 weekly or solvent-based paclitaxel at 200 mg/m^2 once every 3 weeks. Two-thirds of the patients were from Russia and the Ukraine. The rest were from the United States, and, to a lesser extent, Japan and Australia. The patients in the treatment arms were well balanced. The trial met its primary endpoint of showing that the combination of carboplatin and nab-paclitaxel significantly improved the ORR (33% vs 25%; response rate ratio, 1.313; 95% CI, 1.082–1.593; P=.005). Although this was a positive phase III trial, the difference in response did not drive a significant difference in PFS or OS. However, a 10% improvement in PFS and OS was seen.

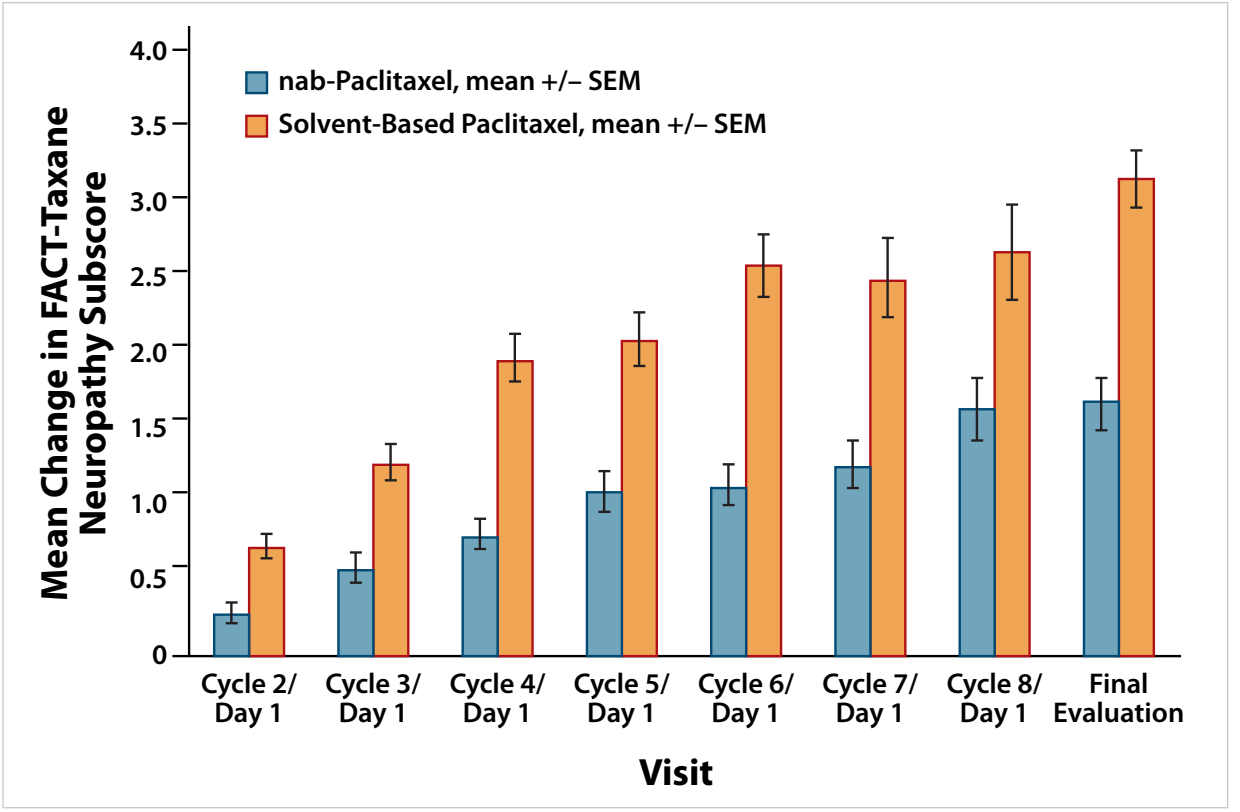

Figure 2. Mean change from baseline in FACT-Taxane neuropathy subscores according to treatment regimen. The figure shows the mean change from baseline to each visit and final evaluation for the sum score of the following 5 questions: I have numbness or tingling in my hands; I have numbness or tingling in my feet; I have trouble buttoning buttons; I have trouble feeling the shape of small objects when they are in my hands; I have pain in my fingertips. FACT=Functional Assessment of Cancer; SEM=standard error of the mean. Reprinted with permission. © 2012 American Society of Clinical Oncology. All rights reserved. Socinski MA et al. *J Clin Oncol*. 30(17), 2012:2055-2062.[23]

Toxicities and Quality of Life

The toxicities differed between the arms of the trial.[23] More grade 3/4 neutropenia occurred in the solvent-based paclitaxel arm compared with nab-paclitaxel (47% vs 58%). Patients in the nab-paclitaxel arm experienced more grade 3/4 anemia (27%) and thrombocytopenia (18%) than patients in the solvent-based paclitaxel arm (6% and <1%, respectively). There were fewer cases of grade 3/4 neuropathy, myalgia, and arthralgia in the nab-paclitaxel arm (3%, <1%, and 0%, respectively) than in the solvent-based paclitaxel arm (11%, 2%, and 2%, respectively). Sensory neuropathy (all grades) was significantly less frequent in the nab-paclitaxel arm (46%) compared with the solvent-based paclitaxel arm (62%; $P<.001$). The percentage of patients who did not develop neuropathy was significantly higher with nab-paclitaxel (54%) than solvent-based paclitaxel (38%; $P<.001$). Among patients who developed grade 3 or higher sensory neuropathy, the median time to improvement to grade 1 was 38 days in the nab-paclitaxel arm and 104 days in the solvent-based paclitaxel arm. Whether the decreased neuropathy in the nab-paclitaxel arm is because nab-paclitaxel is less neuropathic or because the weekly schedule is more favorable remains unknown.

The most common nonhematologic treatment-related adverse events of grade 3 or higher with nab-paclitaxel and solvent-based paclitaxel were fatigue (5% and 6%, respectively), sensory neuropathy (3% and 12%), anorexia (2% and <1%), nausea (<1% and <1%), myalgia (<1% and 2%), and arthralgia (0% and 2%). Among hematologic grade 3 or higher treatment-related adverse events seen with nab-paclitaxel and solvent-based paclitaxel, the most common were neutropenia (47% and 58%), leukopenia (24% and 23%), thrombocytopenia (18% and 9%), and anemia (27% and 7%). Febrile neutropenia occurred in 1% of patients in both arms. There were 2 treatment-related deaths, 1 in each arm.

The Functional Assessment of Cancer Therapy (FACT)-Taxane questionnaire was administered to assess quality of life. Among the intent-to-treat population, 98% completed the questionnaire at baseline, and 94%

had follow-up assessment. As compared with the solvent-based paclitaxel, nab-paclitaxel was associated with significant improvements in the neuropathy subscale (P<.001), the pain subscale (P<.001), and the hearing loss subscale (P=.002; Figure 2). Of note, patients in the nab-paclitaxel arm had fewer interruptions in their daily life.

Influence of Histology

The study also examined the influence of histology.[23] Among patients with squamous NSCLC, nab-paclitaxel was associated with a non-significant improvement in survival of more than 1 month compared with solvent-based paclitaxel (median, 10.7 months vs 9.5 months [HR, 0.890; P=.284]). nab-Paclitaxel was associated with a response rate of 41% in patients with squamous cell NSCLC, which is the highest rate reported in a phase III study in this patient population. The reasons for the higher response rates in squamous NSCLC remain elusive.

Influence of Age

The trial also examined the stratification factor of age.[23] Among the 156 patients who were age 70 years or older, OS was significantly improved in the nab-paclitaxel arm compared with the solvent-based paclitaxel arm (median 19.9 months vs 10.4 months, HR, 0.583; P=.009). This finding was unanticipated, and the reasons for the difference remain uncertain. It may be attributed to the tolerability of nab-paclitaxel.

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Incorporating New Taxanes into First-Line Care of Non–Small Cell Lung Cancer

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In the past, the topic of "new taxanes" implied many new drugs besides paclitaxel and docetaxel, and there has been hope for newer agents in the last several years. In truth, no new taxanes have advanced into the treatment of lung cancer except for nab-paclitaxel. Nab-paclitaxel will likely be incorporated into lung cancer treatment because of the final results from the randomized, phase III trial by Socinski and colleagues that compared nab-paclitaxel with carboplatin versus the standard platinum doublet of paclitaxel and carboplatin, in the first-line setting in patients with advanced NSCLC.[1] This definitive trial also included patients with squamous and non-squamous histologies.

As Dr. Socinski discussed, the trial enrolled 1,052 patients and was designed to examine response rate. The trial had a specified protocol agreement with the FDA, with ORR as the primary endpoint. The secondary endpoints were PFS and OS. For the primary endpoint, the nab-paclitaxel arm had an ORR of 33% versus 25% for the solvent-based paclitaxel arm (P=.005). The secondary endpoints of PFS and OS were essentially the same between the 2 arms; the nab-paclitaxel treatment did not have a survival advantage, but it did have a response rate advantage. Because this phase III study met its primary endpoint, as well as the non-inferiority criteria for PFS and OS, nab-paclitaxel is expected to become a part of first-line NSCLC treatment.

nab-Paclitaxel in the Elderly Patient Subset

The subset analyses from the nab-paclitaxel study are interesting. Although this trial was not restricted to elderly patients, 156 patients ages 70 years and older were enrolled, with 74 in the nab-paclitaxel arm and 82 in the solvent-based paclitaxel arm.[1] nab-Paclitaxel had a nonstatistically significant trend in its favor regarding PFS in the elderly patients, with 8 months versus 6.8 months. The surprising finding was the OS advantage in the elderly patient subgroup. Elderly patients who received nab-paclitaxel had an OS of 19.9 months, as compared to 10.4 months in the solvent-based paclitaxel arm (P=.009).

These data should be interpreted with caution because of the limited number of elderly patients in the study. Nonetheless, it was striking to see a significant OS advantage in a more difficult group of patients to treat. These findings are clinically intriguing, since they suggest that another platinum or taxane-platinum doublet may be available in the first-line setting. Moreover, the regimen may be even more tolerable for older patients. The argument could be made that nab-paclitaxel is probably not inferior to paclitaxel with carboplatin, and that it may be a little better in elderly patients.

nab-Paclitaxel for Squamous Histology

Another finding of interest from this trial was based on histology.[1] Among the 450 patients with squamous NSCLC, the ORR was 41% with nab-paclitaxel compared with 24% with solvent-based paclitaxel (P<.001). The ORR for squamous NSCLC did not translate into an advantage for PFS or OS. Among patients with non-squamous NSCLC, there was no advantage for nab-paclitaxel compared with solvent-based paclitaxel. This suggests that the advantage in ORR for squamous NSCLC may have been driven by squamous histology.

Taxane-Associated Symptoms

The study also examined patient-reported neuropathy and taxane-associated symptoms, and found advantages with nab-paclitaxel compared with solvent-based paclitaxel.[1] According to results from the FACT-Taxane questionnaire, the advantages were statistically significant reductions in patient-reported neuropathy and reductions in hearing loss. nab-Paclitaxel was associated with lower rates of sensory neuropathy (all grades; 46%) than solvent-based paclitaxel (62%; P<.001). nab-Paclitaxel was also associated with higher percentages of patients who did not develop neuropathy (54% vs 38%; P<.001).

These findings are notable. In an era when other agents, such as pemetrexed, are available, paclitaxel has

become a drug that is less favored because it is associated with neuropathy and other toxicities such as arthralgias and myalgias. This trial suggests that nab-paclitaxel is another agent, in addition to pemetrexed, that may be well tolerated in combination with carboplatin.

nab-Paclitaxel Regimen

Many community oncologists and breast physicians have had some experience administering nab-paclitaxel for years, and they have utilized several regimens. However, for the lung cancer indication, the letter of the protocol will need to be followed. The phase III trial used a very specific schedule. Carboplatin was dosed at an AUC of 6 every 3 weeks in a standard way. Nab-paclitaxel was dosed at 100 mg/m^2 weekly without premedication.

Many oncologists use nab-paclitaxel with different schedules. Some will dose it once every 3 weeks at a higher dose, and some will dose it for 2 out of 3 weeks or 3 out of 4 weeks. Those are reasonable regimens for doctors who are comfortable with the different schedules. Notably, it is important to highlight that, in the lung cancer patients in this trial, nab-paclitaxel was given on a weekly schedule with no interruption, and carboplatin was dosed on day 1 every 3 weeks.

nab-Paclitaxel Toxicities

Nab-paclitaxel appears less likely than solvent-based paclitaxel to cause adverse events. However, adverse events do occur. Anemia and thrombocytopenia appear to be more frequent with nab-paclitaxel than with solvent-based paclitaxel. In the study by Socinski and colleagues,[1] nab-paclitaxel was associated with higher rates of grade 3/4 anemia (27%) and thrombocytopenia (18%) than solvent-based paclitaxel (6% and <1%, respectively). nab-Paclitaxel was also associated with fewer cases of grade 3/4 neuropathy, myalgia, and arthralgia (3%, <1%, and 0%, respectively) than solvent-based paclitaxel (11%, 2%, and 2%, respectively). The rate of grade 3/4 neutropenias was lower in the solvent-based paclitaxel arm compared with the nab-paclitaxel arm (47% vs 58%). Fortunately, most oncologists are comfortable managing cytopenias through dose reductions, treatment breaks, or growth factor support. The side effect profile of nab-paclitaxel can be considered manageable.

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Discussion: Emerging Treatment Options in Non–Small Cell Lung Cancer

H&O Are any clinical trials in development for patients with NSCLC?

Mark A. Socinski, MD We are going to follow up on the observation about elderly patients in the nab-paclitaxel trial with a randomized phase II trial. It will be a prospective trial in patients older than 70 years. We are also planning a trial of nab-paclitaxel in combination with radiation therapy in stage III NSCLC. These trials will include the collection of tissue to look for biomarkers, such as caveolin-1 and SPARC.

H&O How might new taxanes change the management of NSCLC?

David Spigel, MD The introduction of a drug like nab-paclitaxel may not dramatically change care in the United States. In patients with non-squamous NSCLC, pemetrexed-based regimens are still quite popular. In patients with squamous NSCLC, the traditional choice in the United States has been gemcitabine-based regimens and paclitaxel and, in some cases, docetaxel-based platinum regimens. Nab-paclitaxel will likely find greater use in patients with squamous NSCLC, although it has not been formally compared with docetaxel or gemcitabine in the first-line lung cancer setting. A doublet regimen of nab-paclitaxel and carboplatin seems to be acceptable, with some safety or toxicity advantages over paclitaxel. One could presume that nab-paclitaxel is going to be at least as favorable as docetaxel in terms of toxicity. Anecdotally, nab-paclitaxel still requires the weekly dosing that adds inconvenience for patients. Doctors who are comfortable with nab-paclitaxel may start using it in non-squamous patients as well. However, it remains to be seen how popular nab-paclitaxel will be for non-squamous NSCLC. We must recognize that reimbursement and cost issues might drive care in certain directions.

H&O How might biomarkers be used in NSCLC?

David Spigel, MD The hottest area now in oncology, not only in lung cancer, is biomarker discovery and trying to subset patients molecularly into more treatable classes of lung cancer. The most obvious are patients with activating EGFR mutations or translocations in the echinoderm microtubule-associated protein-like 4 (EM4) and anaplastic lymphoma kinase (ALK) genes. Much excitement exists regarding *ROS1* rearrangements and RET (rearranged during transfection) rearrangements, which open up potential treatment options for those small subsets of patients.

Dr. Govindan's group and others have been very helpful in providing a lot of these new data. Traditionally, patients with squamous NSCLC have been considered as one group, but in the future, we will have certain subsets that can be treated based on their molecular profile. That is exciting.

The challenge is how to comprehensively test our patients with the minimum amount of material and as quickly as possible so that we can make treatment decisions. The challenge is also in performing clinical trials to help validate discovered biomarkers in these small subsets of patients. That is where we are right now. That is the most exciting part of oncology, and lung cancer is really at the center of it. We have a lot to do but also a lot to be hopeful about.

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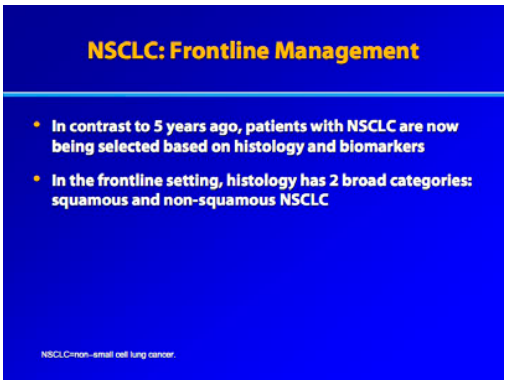

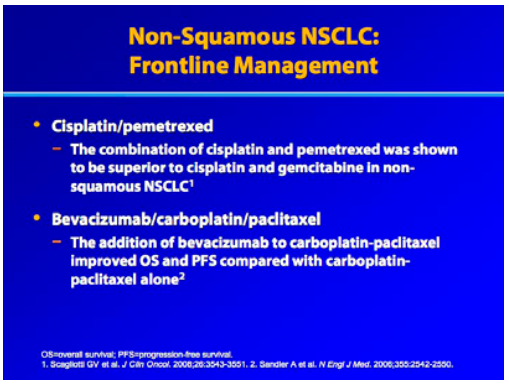

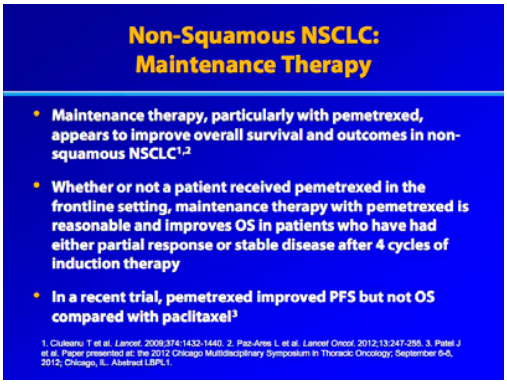

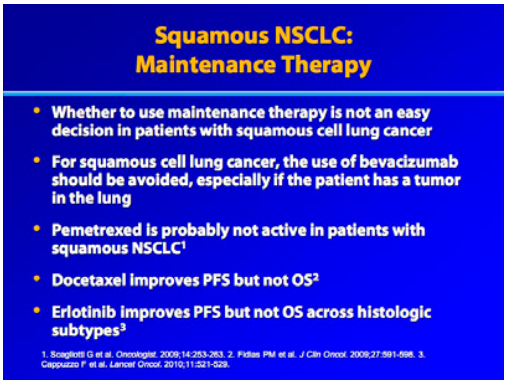

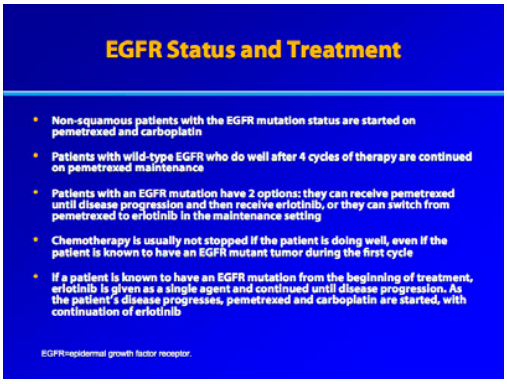

Emerging Taxanes in the First-Line Setting of NSCLC

- The 130 nm albumin-bound formulation of paclitaxel (also known as nab®-paclitaxel [Abraxane®, Celgene, Summit, NJ]) has been available for breast cancer therapy for several years, based on randomized clinical trial data showing an advantage over other taxanes
- Compared with solvent-based paclitaxel, nab-technology uses albumin to deliver paclitaxel to tumors, resulting in 10-fold higher mean C_{max} of free paclitaxel,[1] delivery of 33% higher drug concentration to tumors in preclinical xenograft models,[2] and enhanced transport across endothelial cell monolayers[2]
- The use of albumin dispenses the need for solvents, which have been shown to limit drug bioavailability by entrapping drug in micelles[3-5]

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Nab-Paclitaxel in NSCLC: Phase III Clinical Trial Data[1]

- A total of 1,052 untreated patients with stage IIIB to IV NSCLC received carboplatin at an AUC of 6 every 3 weeks. Patients were then randomly assigned to receive nab-paclitaxel at 100 mg/m² weekly or solvent-based paclitaxel at 200 mg/m² once every 3 weeks
- The trial met its primary endpoint of showing that the combination of carboplatin and nab-paclitaxel significantly improved the ORR (33% vs 25%; response rate ratio, 1.313; 95% CI, 1.082–1.593; *P*=.005)
- Although this was a positive phase III trial, the difference in response did not drive a significant difference in PFS or OS. However, a 10% improvement in PFS and OS was seen

AUC=area under the curve; ORR=overall response rate; CI=confidence interval.
Socinski MA et al. *J Clin Oncol.* 2012;30:2055-2062.

Influence of Age and Histology in a Phase III Trial[1]

- Among the 156 patients who were 70 years or older, OS was significantly improved in the nab-paclitaxel arm compared with the solvent-based paclitaxel arm (median 19.9 months vs 10.4 months, HR, 0.583; *P*=.009)
- Among patients with squamous NSCLC, nab-paclitaxel was associated with a non-significant improvement in survival of more than 1 month compared with solvent-based paclitaxel (median, 10.7 months vs 9.5 months [HR, 0.890; *P*=.284])

Socinski MA et al. *J Clin Oncol.* 2012;30:2055-2062.

Nab-Paclitaxel vs Solvent-Based Paclitaxel: Toxicities in a Phase III Trial[1]

More Common With Solvent-Based Paclitaxel	More Common With Nab-Paclitaxel
Grade 3/4 neuropathy Grade 3/4 neutropenia Grade 3/4 myalgia Grade 3/4 arthralgia Pain Hearing loss interruptions in daily life Sensory neuropathy (all grades)	Grade 3/4 anemia Grade 3/4 thrombocytopenia

Socinski MA et al. *J Clin Oncol.* 2012;30:2055-2062.

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