

Therapeutic advances in non-small cell lung cancer: Highlights from the annual clinical cancer conferences

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Treatment of advanced non-small cell lung cancer is in the midst of a paradigm shift. Recent efforts have focused on incorporating newer agents into first-line chemotherapy regimens and first-line maintenance therapy. These strategies have resulted in improvements in outcomes for certain patient subgroups, leading the way toward more individualized treatment. As a result, first-line therapy is increasingly being selected based on clinical characteristics, histology, and molecular markers. Several ongoing trials are prospectively investigating histology and molecular characteristics with the goal of further optimizing treatment.

An efficacy plateau has been reached with conventional platinum-based doublet chemotherapy regimens as first-line treatment for advanced non-small cell lung cancer (NSCLC),¹ underscoring the need for new strategies. Over the past decade, several therapeutic options for relapsed NSCLC were introduced. New agents include the novel antifolate pemetrexed and the molecularly targeted agents bevacizumab and erlotinib.² This article reviews lessons learned from randomized trials regarding the optimal use of these newer agents as first-line therapy and maintenance therapy. Based on these data, since published, ongoing trials are further evaluating the optimal use of these and other promising agents in the management of patients with advanced NSCLC.

Updated lung cancer staging system

The American Joint Committee on Cancer (AJCC) staging system for lung cancer is periodically evaluated for relevance in light of changes in diagnostic capabilities and treatment options. Successive iterations of the AJCC tumor-node-metastasis (TNM) staging system have addressed such shortcomings as they arose. For example, patients within the same stage group may have different prognoses, making it difficult for clinicians to select appropriate treatment.

To guide future revisions of the TNM system, the International Association for the Study of Lung Cancer (IASLC) utilized an international

registry comprising tens of thousands of lung cancer patients, pairing presentation with ultimate outcomes. As a consequence, in 2007 the IASLC Lung Cancer Staging Project recommended substantial changes to the TNM staging system (Table 1).³⁻⁵ Despite the increased complexity of this staging system, three major changes are noteworthy, as they may influence the selection of appropriate treatment for patients with NSCLC:

- *TNM stages T1 and T2.* The T1 category, which previously categorized tumors up to 3 cm in size, has now been subdivided into T1a (up to 2 cm) and T1b (2–3 cm). This change reflects differences in the surgical outcomes of patients in the T1a and T1b categories. Also based on differential prognosis, T2 has been divided into three separate categories: T2a (3–5 cm), T2b (5–7 cm), and T3 (≥ 7 cm).
- *Ipsilateral lung nodules.* It has been recognized that ipsilateral nodules may be managed surgically and are not necessarily in the domain of advanced or metastatic disease. Thus, what used to be recognized as a same-lobe nodule T4 is now considered T3, based on its resectability. Also, what used to be recognized as M1 (ipsilateral lung nodule in a separate lobe) is now considered T4, again acknowledging the fact that many of these patients can be approached surgically.
- *Pleural and pericardial effusions.* Recognizing that prognosis can be different among patients with metastatic disease, this group has been separated into M1a and M1b based on whether the metastasis is intrathoracic or more distant (extrathoracic). What

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TABLE 1
Updated lung cancer staging system (IASLC 2007)³⁻⁵

UICC6 T/M descriptor	Proposed T/M	N0	N1	N2	N3
T1 (≤2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (>2-3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (3 to ≤5 cm)	T2a	IB	IIA (IIB)	IIIA	IIIB
T2 (>5-7 cm)	T2b	IIA (IB)	IIB	IIIA	IIIB
T2 (≥7 cm)	T3	IIB (IB)	IIIA (IIB)	IIIA	IIIB
T3 (invasion)	T3	IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)	T3	IIB (IIIB)	IIIA (IIIB)	IIIA (IIIB)	IIIB
T4 (extension)	T4	IIIA (IIIB)	IIIA (IIIB)	IIB	IIIB
M1 (ipsilateral lung)	T4	IIIA (IV)	IIIA (IV)	IIIB (IV)	IIIB (IV)
T4 (pleural effusion)	M1a	IV (IIIB)	IV (IIIB)	IV (IIIB)	IV (IIIB)
M1 (contralateral lung)	M1a	IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

UICC6 = Union Internationale Contre le Cancer (International Union Against Cancer); TNM classification of malignant tumors, 6th edition; T/M = tumor/metastasis
Stages highlighted in color are changed from the previous designation (shown in parentheses).

used to be recognized as “wet IIIB T4” (ie, with pleural or pericardial effusion) is now designated as M1a, a categorization that also includes contralateral lung involvement. So, for instance, T4 malignant pleural effusions, which in the past would have been considered stage IIIB and would have caused quite a bit of confusion with “dry” stage IIIB, are now designated stage IV because they are treated similarly to other presentations of stage IV disease.

First-line considerations for advanced NSCLC

Standard front-line chemotherapy for NSCLC consists of a platinum-based doublet, with the nonplatinum component selected based on disease histology.^{1,2,6-8} Gemcitabine- or tax-

ane-containing doublets are preferred for squamous cell carcinoma, whereas pemetrexed-containing doublets are preferred for non-squamous cell carcinoma, including adenocarcinoma. Bevacizumab may be added to front-line chemotherapy in patients with nonsquamous carcinoma and no evidence of antecedent hemoptysis; brain metastasis, if present, must be treated first before these patients can receive bevacizumab. Based on the FLEX trial data, which showed a survival advantage, cetuximab may potentially have a role in the front-line setting when added to platinum-based chemotherapy. Traditionally, initial chemotherapy regimens were administered for 4-6 cycles, based on studies that showed no additional clinical

benefit with further treatment.⁹

An increasing number of factors need to be taken into account when considering appropriate first-line treatment for a patient diagnosed with advanced NSCLC. In addition to standard prognostic factors, including performance status (PS), gender, comorbidity, and weight loss, it is important to consider the validity of the histologic diagnosis, as this is often limited by small sample size (Figure 1). Historically, pathologists were asked to differentiate only between small cell and non-small cell carcinoma, but they are now asked to go a step farther and differentiate between squamous and nonsquamous NSCLC using both histologic assessment and special immunohistochemical stains.

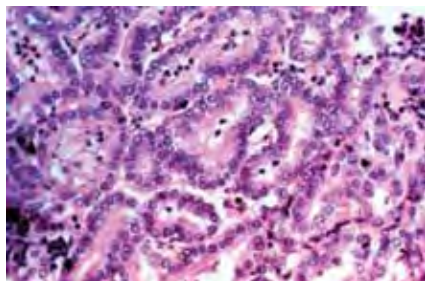
It is also critical to establish whether sufficient tumor tissue (ie, biopsy vs fine-needle aspirate) is available for other special studies that may influence treatment decisions, including molecular assessments, such as epidermal growth factor receptor (EGFR) mutation status or echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) status.⁶

When treatment options are considered, individual patients need to be assessed for their optimal chemotherapy regimen, as well as their eligibility for targeted or genotypically driven therapies.

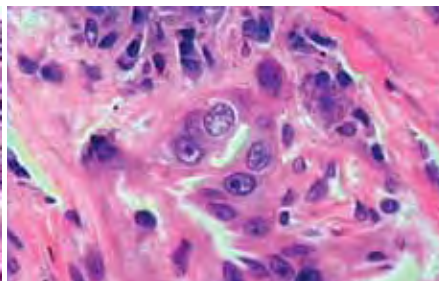
Chemotherapy

A landmark trial conducted by the Eastern Cooperative Oncology Group

Adenocarcinoma



Large cell



Squamous

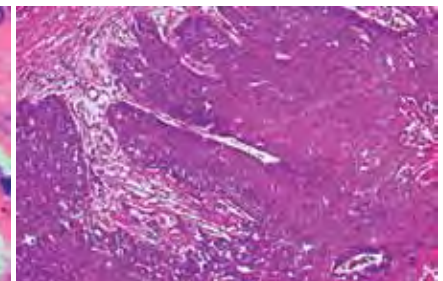
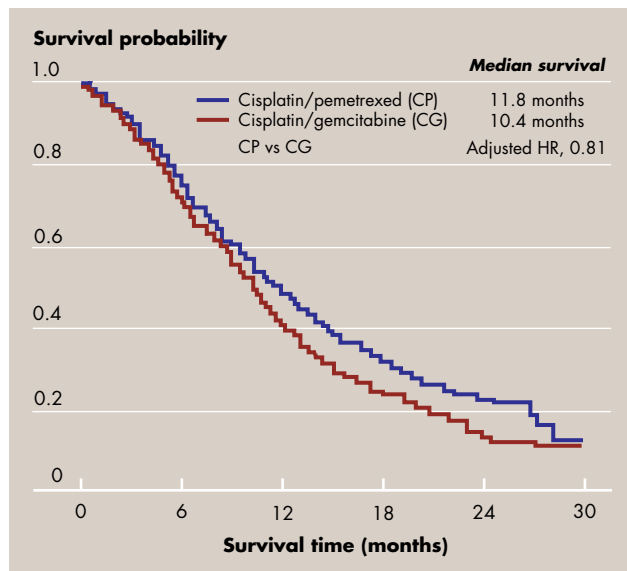


FIGURE 1 Non-small cell lung cancer histology represents a spectrum of differentiation.

Nonsquamous histology



Squamous cell carcinoma

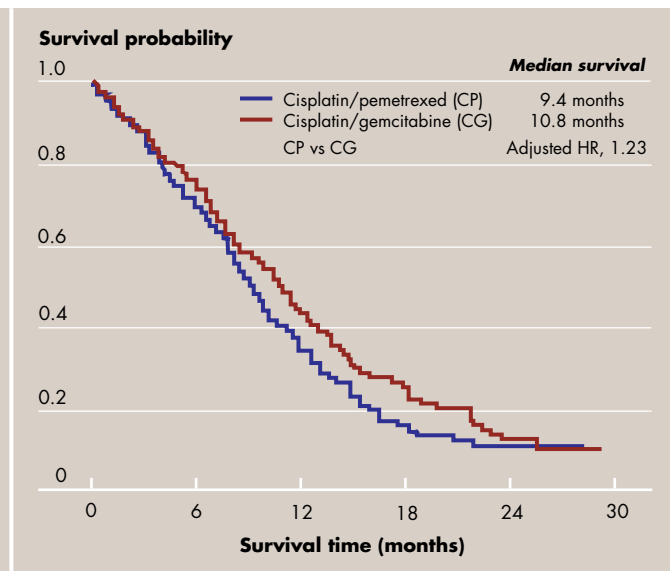


FIGURE 2 Cisplatin/pemetrexed versus cisplatin/gemcitabine in non-small cell lung cancer (NSCLC): overall survival by NSCLC histology. HR = hazard ratio. Adapted, with permission, from Scagliotti et al.¹⁰ © 2008 American Society of Clinical Oncology. All rights reserved.

(ECOG 1594) compared three third-generation doublet regimens (cisplatin plus gemcitabine, cisplatin plus docetaxel, and carboplatin plus paclitaxel) with a “standard” regimen, cisplatin plus paclitaxel, and found no difference in response or survival among the four regimens.¹

More recently, Scagliotti et al conducted a very large trial in more than 1,700 patients to evaluate a newer third-generation nonplatinum partner (pemetrexed) plus cisplatin compared with gemcitabine plus cisplatin.¹⁰ This noninferiority trial showed no difference in survival in the intent-to-treat population. However, because the primary target of pemetrexed (thymidylate synthase [TS]) is expressed differentially depending on histologic type, it was thought that the drug might be more efficacious in patients with adenocarcinoma. Indeed, a preplanned subset analysis showed that patients with non-squamous cell NSCLC benefited more from the pemetrexed-containing regimen (hazard ratio [HR] for death, 0.84; 95% confidence interval [CI], 0.71, 0.99; $P = 0.03$; Figure 2).¹⁰ In contrast, those patients with squa-

mous cell NSCLC fared better with cisplatin plus gemcitabine.

On the basis of these results, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved pemetrexed plus cisplatin as a first-line regimen only in patients with a non-squamous histology. Consequently, we can no longer assume that all platinum-based doublets are equivalent with regard to efficacy in patients with advanced NSCLC. Certainly, histology must be considered in choosing the optimal agents for individual patients. For those patients with advanced adenocarcinoma (or nonsquamous carcinoma) of the lung and a good PS, cisplatin/pemetrexed is a preferred regimen, compared with cisplatin/gemcitabine, based on noninferiority and decreased toxicity.

Preventive strategies for management of some of the toxicities associated with pemetrexed have been developed.¹¹ Oral folic acid (350–1,000 $\mu\text{g}/\text{d}$ beginning 1 week prior to pemetrexed administration) and vitamin B₁₂ (1,000 μg intramuscularly 0–7 days prior to pemetrexed) significantly reduce marrow and muco-

sal toxicities, particularly diarrhea and mucositis. This preemptive strategy has made a potentially toxic drug far less toxic and has virtually eliminated the clinical sequelae of myelosuppression and diarrhea. Also, rash may be prevented or reduced by oral dexamethasone given the day before, the day of, and the day after pemetrexed. Alternatively, intravenous dexamethasone may be given on the day of pemetrexed administration.

Bevacizumab

The vascular endothelial growth factor (VEGF) pathway is an important regulator of tumor angiogenesis.¹² Bevacizumab, a recombinant humanized monoclonal antibody against VEGF, has demonstrated clinical activity in different types of human cancer, particularly NSCLC. Although there are a number of agents that inhibit the VEGF pathway by alternative mechanisms—by inhibiting VEGF receptor tyrosine kinase activity (eg, sunitinib, sorafenib)—bevacizumab remains the only approved VEGF inhibitor for NSCLC at this time. The indication for bevacizumab is limited to patients with nonsqua-

TABLE 2

ECOG 4599 trial of bevacizumab in combination with first-line chemotherapy in patients with a nonsquamous NSCLC histology¹⁴

Endpoint	CbT (n = 444)	CbT + bevacizumab (n = 434)	Hazard ratio (95% CI)	P value
Response rate, %	35	15	–	<0.001
Progression-free survival, months	4.6	6.2	0.66 (0.57, 0.77)	<0.001
Overall survival, months	10.3	12.3	0.79 (0.67, 0.92)	0.003

ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer; CbT = carboplatin plus paclitaxel; CI = confidence interval

mous NSCLC, based on patient safety considerations.

A randomized phase II study indicated that patients with a squamous cell histology have an untoward risk of pulmonary hemorrhage with use of bevacizumab.¹³ ECOG conducted a phase III randomized study (E4599) comparing carboplatin/paclitaxel alone with carboplatin/paclitaxel plus bevacizumab (15 mg/kg) in patients with recurrent or advanced nonsquamous NSCLC (Table 2).¹⁴ This trial explicitly excluded patients with brain metastases; clinically significant hemoptysis; uncontrolled hypertension; a history of documented hemorrhagic diathesis or coagulopathy; therapeutic anticoagulation; regular use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), or other agents known to inhibit platelet function; and inadequate organ function or a poor PS.

With the addition of bevacizumab, the median overall survival (OS) improved from 10.3 months to 12.3 months (HR, 0.79; 95% CI, 0.67, 0.92; $P = 0.003$). The Kaplan-Meier curves for OS showed an early separation, consistent with a difference of 7%–8%, which persisted for at least 1–2 years. In this study, bevacizumab was continued until disease progression (continuation maintenance). A significant improvement in progression-free survival (PFS; $P < 0.001$) was also demonstrated, as well as a better response rate ($P < 0.001$), favoring the bevacizumab-containing arm. In a separate analysis by Wake-

lee and colleagues, men of any age derived a survival benefit, whereas a survival improvement was limited to women under the age of 60.¹⁴

The addition of bevacizumab was generally well tolerated, although the combination is more toxic than chemotherapy alone.¹⁵ Hemorrhage and hypertension were among the adverse events occurring more frequently in the bevacizumab arm than in the control arm ($P < 0.001$). There were no significant differences in either venous or arterial thrombosis. Bevacizumab also yielded an increased risk of myelosuppression and neutropenic fever in combination with chemotherapy compared with chemotherapy alone. There was a significant difference ($P = 0.001$) in treatment-related deaths, principally related to bleeding (hemoptysis, gastrointestinal [GI]) in the bevacizumab-containing arm. In clinical practice, the biggest concern with bevacizumab is bleeding; hypertension can be managed with the use of antihypertensives or by delaying the next cycle.

In the E4599 trial, some of the deaths were due to febrile neutropenia, primarily in patients over the age of 70 years.¹⁵ Therefore, the safety of this bevacizumab-containing regimen in elderly patients was explored further. In a retrospective analysis, patients who were 70 years of age or older had worse-grade toxicity and significant increases in neutropenia, GI bleeding, proteinuria, muscle weakness, motor neuropathy, and dizziness.¹⁶ However, in the postapprov-

al registry ARIES study with a large number of patients, those older than 70 years and those older than 80 years did not appear to have a numerically increased rate of grade 3 or 4 bleeding events compared with younger patients.¹⁷ This finding is somewhat reassuring with regard to safety based upon age. Nevertheless, because there are some safety concerns about the use of bevacizumab in NSCLC patients, it is important to be selective when using this agent in patients over age 70.

Patients with brain metastases were excluded from the E4599 trial. However, given the fact that about 17%–18% of patients diagnosed with NSCLC present with brain metastasis and many more patients develop brain metastases during the course of their disease, it was important to establish the safety of bevacizumab in this population. The PASSPORT trial¹⁸ (a phase II trial that looked specifically at the rate of central nervous system [CNS] hemorrhage in both the first- and second-line settings); the ATLAS maintenance trial¹⁹; and the ARIES registry study¹⁷ all included patients with treated brain metastases if the metastases were deemed to be controlled as a result of that treatment.

A review of these studies showed the composite rate of CNS hemorrhage to be quite low, at 1.1%.¹⁸ Similarly, the CNS hemorrhage rate was about 1% in the SAiL trial, a European registry study that included only patients who were known to have no brain metastases.²⁰ The available data suggest strongly that in those patients who have effectively treated and controlled brain metastases, it may be safe to use bevacizumab as long as there are no other contraindications.

Patients needing therapeutic anticoagulation were excluded from the E4599 trial. However, in the AVAiL study, full-dose anticoagulation was permitted for treatment of venous thromboembolism that may have oc-

TABLE 3

Comparison of efficacy outcomes in two phase III trials of cetuximab in advanced NSCLC^{25,26}

Endpoint	FLEX ²⁵			BMS099 ²⁶		
	CisV (n = 568)	CisV + cetuximab (n = 557)	P value (HR) or Δ	CbT (n = 338)	CbT + cetuximab (n = 338)	P value (HR) or Δ
Response rate, %	29.2	36.3	0.12	17.2	25.7	0.006
Median PFS, months	4.8	4.8	0.38 (HR, 0.94)	4.4	4.2	0.23 (HR, 0.90)
Median OS, months	10.1	11.3	0.04 (HR, 0.87)	8.4	9.7	0.17 (HR, 0.89)
One-year survival, %	42	47	Δ 5%	40	45	Δ 5%

NSCLC = non-small cell lung cancer; CisV = cisplatin plus vinorelbine; HR = hazard ratio; Δ = magnitude of difference between two treatment arms; CbT = carboplatin plus paclitaxel; PFS = progression-free survival; OS = overall survival

curred subsequent to study enrollment. An analysis of these patients relative to those who were not anticoagulated suggests a slight increase in the rate of all-grade bleeding, but the occurrence of grade 3 or 4 bleeding was similar.²¹ None of the patients receiving full-dose anticoagulation experienced grade 3 or higher hemoptysis. These data suggest that, if needed, therapeutic anticoagulation may be administered safely in patients receiving bevacizumab, again assuming that there are no other contraindications to this class of agents.

Because both pemetrexed and bevacizumab are indicated for the non-squamous population, the potential for combining these agents in first-line treatment is being explored. A phase II trial evaluated carboplatin plus pemetrexed plus bevacizumab for 6 cycles in 50 patients, with continued maintenance of pemetrexed plus bevacizumab in nonprogressing patients. The results of this small, single-arm study were encouraging, with an overall response rate of 55%, a median PFS of 7.8 months, and a median OS of 14.1 months.²²

The PointBreak (JMHD) trial,²³ an ongoing phase III trial, is comparing the carboplatin/pemetrexed/bevacizumab regimen (with combination pemetrexed/bevacizumab as maintenance) with the regimen used in the E4599 study: carboplatin/paclitaxel/bevacizumab (with bevacizumab continued as maintenance). This will be the first direct comparison of pemetrexed and paclitaxel in beva-

cizumab-eligible patients. The trial has completed accrual, randomizing approximately 900 patients. Overall survival is the primary endpoint. Efficacy results are not expected for some time, but results on safety and other aspects of the trial are anticipated during the next year or two.

EGFR inhibitors

The EGFR signaling pathway has a key role in cancer cell proliferation and tumor invasion.²⁴ Several therapies designed to inhibit this pathway have shown activity in NSCLC, including small-molecule EGFR tyrosine kinase inhibitors (eg, erlotinib and gefitinib) and monoclonal antibodies (eg, cetuximab).

Cetuximab. Cetuximab, a monoclonal antibody against EGFR, has been combined with chemotherapy in two randomized phase III trials in patients with advanced NSCLC (Table 3).^{25,26} In the FLEX trial,²⁵ chemotherapy-naïve patients with EGFR-expressing NSCLC, as detected by immunohistochemistry, were randomized to receive cisplatin plus vinorelbine chemotherapy with or without cetuximab. The addition of cetuximab was associated with an improved median OS of 11.3 months vs 10.1 months with chemotherapy alone (HR, 0.87; 95% CI, 0.762, 0.996; $P = 0.044$). The main added toxicity was acne-like rash, with grade 3 rash developing in 10% of patients. Patients in the cetuximab arm also had a higher occurrence of grade 3 or 4 febrile neutropenia (but not neutro-

penia), diarrhea, and infusion-related reactions ($P < 0.05$).

The BMS099 trial,²⁶ which evaluated the addition of cetuximab to carboplatin plus taxane chemotherapy as first-line treatment of NSCLC, did not meet its primary endpoint of improved PFS. However, there was a trend toward improved OS (a secondary endpoint) with the addition of cetuximab to chemotherapy (HR, 0.89; 95% CI, 0.75, 1.05; $P = 0.17$). It is possible that the smaller size of the BMS099 trial may account for its inability to yield a significant difference in OS.

In both the FLEX and BMS099 trials, there was a significant difference in response rate favoring cetuximab of about the same magnitude. However, there was no difference in PFS, which was not the primary endpoint in FLEX. With regard to OS, in both trials there was a similar magnitude of difference in median 1-year survival (vs the control arm), and HRs for death were almost identical. Therefore, results from these two trials seem to be superimposable, even though one was considered "positive" and the other "negative."

Thatcher and colleagues performed a meta-analysis of four randomized, controlled trials that have independently reported improvements in survival for platinum-based chemotherapy regimens combined with cetuximab as first-line therapy in patients with advanced NSCLC.²⁷ This analysis confirmed the clinical benefits of cetuximab for OS, PFS,

and objective response rate (ORR) and found no differences in treatment benefit across the studies. Whether cetuximab will gain approval for first-line treatment of NSCLC remains to be seen.

An ongoing randomized phase III trial conducted by the Southwest Oncology Group (S0819)²⁸ is evaluating the addition of cetuximab to first-line carboplatin, paclitaxel, and bevacizumab, with PFS as the primary endpoint. This trial includes correlative science, with the goal of identifying a biomarker to better predict which patients may benefit most from cetuximab in this setting.

Gefitinib and erlotinib. In contrast to the cetuximab trials, the addition of gefitinib or erlotinib to first-line platinum-based chemotherapy doublets has not resulted in improved survival in randomized phase III trials of unselected patients (INTACT 1 and INTACT 2 with gefitinib; TRIBUTE and TALENT with erlotinib).^{29–32} However, the phase II single-agent trial experience with both gefitinib and erlotinib revealed certain clinical characteristics that were predictive of response. They include a history of never smoking, adenocarcinoma histology (especially with bronchoalveolar features), female gender, and Asian ethnicity. All of these clinical factors enrich for the presence of activating mutations (exon 19 deletion or exon 21 insertion) in the EGFR gene, which were revealed to be present in patients who experienced dramatic responses to these agents. Subsequently, these characteristics were prospectively assessed in a series of phase II trials of gefitinib or erlotinib in selected patients with advanced NSCLC. Most notably, response rates of 70%–80% were reported in studies that enrolled only patients with activating EGFR mutations (reviewed by Tiseo et al⁷).

More recently, a phase III trial conducted in Asia (IPASS) compared first-line therapy with gefitinib

to carboplatin plus paclitaxel chemotherapy in never or light smokers with advanced NSCLC.³³ In this noninferiority trial, there was a highly statistically significant improvement in PFS, the primary endpoint, for those receiving gefitinib (HR, 0.74; 95% CI, 0.65, 0.85; $P < 0.001$). Higher response rates were also observed with gefitinib (43% vs 32%; $P = 0.0001$). There was no difference in OS, but this may be due, in part, to patients on the chemotherapy arm receiving gefitinib as subsequent therapy.

An important aspect of the IPASS trial was the exploratory evaluation of biomarkers. Of the 1,217 patients enrolled, 437 had tumor tissue available for molecular analysis. When PFS was analyzed according to EGFR mutation status, it became evident that the PFS was significantly longer with gefitinib than with chemotherapy only for those patients with activating EGFR mutations (HR, 0.48; 95% CI, 0.36, 0.64; $P < 0.001$).³³ Conversely, patients who were EGFR mutation-negative or wild type did poorly on gefitinib, and their PFS was significantly longer with chemotherapy ($P < 0.001$). These results indicate that the benefit of first-line gefitinib versus chemotherapy is based on EGFR mutation status.

Whereas the IPASS trial selected patients based on phenotype, the Japanese NEJ002 study³⁴ selected patients based on genotype. Only patients with activating EGFR mutations (primarily exon 19 and exon 21 mutations) and the absence of

the T790M EGFR mutation (which is associated with gefitinib resistance) were enrolled (Table 4).³⁴ Patients were randomized to receive either gefitinib or carboplatin plus paclitaxel chemotherapy as first-line treatment. Again, a significant PFS advantage was demonstrated with gefitinib in this EGFR mutation-positive population, with a doubling of median PFS to 10.8 months versus 5.4 months with chemotherapy (HR, 0.30; 95% CI, 0.22, 0.41; $P < 0.001$). There was about a 15% difference in 2-year survival in those patients receiving gefitinib compared with those on carboplatin/paclitaxel and a trend toward improved OS favoring gefitinib, although the difference was not statistically significant.

In the open-label, phase III Japanese WJTOG3405 study,³⁵ 177 chemotherapy-naïve, EGFR mutation-positive (either the exon 19 deletion or L858R point mutation) patients aged 75 years or younger were randomized to receive either gefitinib (250 mg/d orally; $n = 88$) or cisplatin plus docetaxel ($n = 89$). PFS was significantly longer for gefitinib (9.2 months vs 6.3 months for chemotherapy; $P < 0.0001$).

The phase III OPTIMAL study randomized 165 EGFR mutation-positive patients to receive front-line therapy with either erlotinib, 150 mg/d ($n = 83$), or gemcitabine plus carboplatin ($n = 82$).³⁶ Median PFS was 13.1 months in the erlotinib arm compared with 4.6 months in the chemotherapy arm. The ORR with erlo-

TABLE 4

NEJ002 (Japan): phase III trial of gefitinib versus chemotherapy for EGFR mutation-positive advanced NSCLC³⁴

Endpoint	Gefitinib (n = 115)	CbT (n = 115)	HR (95% CI)
Median PFS, ^a months	10.8	5.4	0.30 (0.22, 0.41)
Two-year PFS	8.4%	0%	–
Median OS, months	30.5	23.6	0.31 (NR)
Two-year OS	61.4%	46.7%	–

NSCLC = non-small cell lung cancer; CbT = carboplatin plus paclitaxel; HR = hazard ratio; PFS = progression-free survival; OS = overall survival; NR = not reported

^aPrimary endpoint

tinib was 83% compared with 36% for chemotherapy. Although this study mirrored the results of the NEJ002 and WJTOG3405 trials with gefitinib, the OPTIMAL study is the first reported prospective phase III study to confirm the role of erlotinib in advanced NSCLC patients with activating EGFR mutations. An ongoing phase III trial (EURTAC-SLCG) is comparing first-line erlotinib versus platinum-based doublet chemotherapy in a Caucasian population selected for patients with nonsquamous NSCLC and exon 19 or exon 21 EGFR mutations.³⁷ Results are not yet available from this important trial.

Rash and diarrhea are common adverse effects associated with gefitinib and erlotinib therapy, but they can often be managed preemptively. Various approaches may be taken to prevent or lessen the severity of the rash, including using a moisturizing face lotion containing sunscreen and minimization of sun exposure; taking the drug on an empty stomach (eg, at night); and utilizing prophylactic oral antibiotics (eg, minocycline [100 mg twice daily on a 2 weeks on, 2 weeks off schedule] or doxycycline). Topical hydrocortisone (1%) may be used to treat grade 1 or 2 rash, whereas oral antibiotics (eg, clindamycin) or steroids can be given to mitigate grade 2 or 3 rash. This approach generally prevents the development of grade 3 acneiform rash, improving the tolerability of these agents. Diarrhea should be treated preemptively at the first hint of loose bowel movements.

Individualizing first-line therapy

It is believed that about one-third of NSCLC patients who have EGFR wild-type tumors and a light or no smoking history are positive for the EML4-ALK fusion protein.⁷ Relative to those without ALK rearrangements, these patients appear to have resistance to small-molecule EGFR tyrosine kinase inhibitors but similar

Case study #1

A 55-year-old woman presents with cough and mild shortness of breath. She says she smoked in college but not since (4 pack-years). Her chest x-ray shows a 4-cm right upper lobe mass with multiple bilateral pulmonary nodules. CT scan confirms these findings plus a right adrenal nodule. Brain MRI is negative, and she ends up having a core biopsy of the mass that shows moderately differentiated adenocarcinoma.

Which of the following tests would you want to obtain?

1. EGFR mutation
2. KRAS mutation
3. EML4-ALK
4. All of the above
5. 1 and 3

At present, the only validated biomarker for individualizing first-line treatment of advanced NSCLC is the presence of an activating EGFR mutation. EGFR protein positivity by immunohistochemistry and EGFR gene copy number measured by fluorescence in situ hybridization have been studied in clinical trials, but their predictive value remains uncertain. Similarly, KRAS mutation has appeared to be a negative predictor of response to EGFR tyrosine kinase inhibitors in some, but not all, studies.

outcomes with first-line chemotherapy. However, because these tumors appear to be responsive to ALK inhibition, this biomarker may become more important for patient selection in the future. A phase III trial evaluating the ALK inhibitor crizotinib in patients with ALK-rearranged NSCLC is under way (ClinicalTrials.gov ID No. NCT00932893). Similarly, there are currently no approved agents that target mutated KRAS, but the role of KRAS continues to be studied.

There are other potential predictive markers of sensitivity to chemotherapy agents, such as endonuclease excision repair cross-complementing group 1 (ERCC1) for platinum, ribonucleotide reductase subunit M1 (RRM1) for gemcitabine, and TS for pemetrexed-based therapy. These markers are not yet validated but are certainly intriguing.

In case study #1, most physicians would at least determine the EGFR mutation status to guide appropriate first-line treatment. Some would also

consider obtaining EML4-ALK and KRAS status at presentation, as these may be informative in the future.

Maintenance therapy in advanced NSCLC: state of the art or state of confusion?

For patients without disease progression after first-line treatment, maintenance therapy is an option. However, no clear standard yet exists. The goal of maintenance therapy is to extend the duration of response or stable disease for as long as possible, ultimately improving survival. There are different forms of maintenance therapy. Continuation maintenance retains a component of the original regimen, usually the nonplatinum partner. In contrast, “switch” maintenance features a new agent in the absence of disease progression.

Pemetrexed and erlotinib are approved in the United States for use as switch maintenance therapy, based on survival advantages demonstrated

TABLE 5

Maintenance therapy options based on histology and EGFR mutation status^{2,38,39}

Adenocarcinoma	Squamous cell	EGFR mutation
Erlotinib ^a	Erlotinib ^a	Erlotinib ^{a,b}
Gefitinib	Gemcitabine	Gefitinib
Pemetrexed ^a	Docetaxel	
Bevacizumab		

^aFDA approved in the maintenance setting for advanced non-small cell lung cancer

^bIn the SATURN trial, erlotinib was active both in patients with activating EGFR mutations (hazard ratio [HR], 0.10; 95% confidence interval [CI], 0.04, 0.25; $P < 0.0001$) and in those with wild-type EGFR (HR, 0.78; 95% CI, 0.63, 0.96; $P = 0.0185$).³⁹

in the JMEN³⁸ and SATURN³⁹ trials, respectively (Table 5).^{2,38-40} Docetaxel, gemcitabine, bevacizumab, and gefitinib have also been studied in the first-line maintenance setting.

The modern era of first-line maintenance therapy for advanced NSCLC was introduced by Fidias and colleagues in a phase III trial that evaluated immediate (switch maintenance) versus delayed (at disease progression) docetaxel in patients who had an objective response or stable disease with 4 cycles of carboplatin and gemcitabine.⁴⁰ Of 566 patients enrolled in the study, 309 were randomized after completing their chemotherapy, but only about 60% of those who were assigned to the delayed docetaxel arm actually received this treatment. There was a significant improvement in PFS with a very robust P value ($P = 0.0001$) favoring immediate maintenance therapy. The median PFS dou-

bled from 2.7 months in the delayed arm to 5.7 months in the immediate maintenance arm. The difference in OS, the primary endpoint, however, was not statistically significant ($P = 0.085$), although there was a numerical advantage for immediate therapy with respect to 1-year survival (51.1% vs 43.5%). It is possible that this trial may simply have been underpowered to demonstrate a difference in OS.

The therapeutic paradigm for first-line maintenance therapy was likely changed by the results from the JMEN trial,³⁸ which compared maintenance pemetrexed with placebo in patients who responded or had stable disease after 4 cycles of standard platinum-based doublet chemotherapy. Patients in both arms also received vitamin B₁₂, folate, and dexamethasone. The randomization actually occurred after stabilization or response had been documented. Patients were further stratified according to gender, PS, stage, nature of the tumor response, which non-platinum drug was partnered with platinum, and the absence or presence of brain metastases.

Pemetrexed significantly improved the primary endpoint of PFS (HR, 0.50; 95% CI, 0.42, 0.61; $P < 0.0001$). When analyzed by histology, the PFS benefit of pemetrexed maintenance was seen in patients with nonsquamous histology (HR, 0.47; 95% CI, 0.37, 0.6; $P < 0.00001$) (Table 6).³⁸ In this subgroup, pemetrexed mainte-

nance more than doubled the median PFS (4.4 months vs 1.8 months for placebo). This benefit translated to an OS advantage for patients with nonsquamous NSCLC, especially adenocarcinoma. In contrast, patients with squamous histology obtained absolutely no PFS or OS benefit from pemetrexed maintenance. In the intent-to-treat population, pemetrexed maintenance yielded an OS advantage of about 2.8 months (HR, 0.79; 95% CI, 0.65, 0.95; $P = 0.012$), presumably due to the fact that the majority of patients enrolled in this study had a nonsquamous histology.

As opposed to switch maintenance, continuation maintenance with pemetrexed is currently being studied in patients with nonsquamous NSCLC in the Paramount trial.⁴¹ This study is being conducted in Europe and is comparing pemetrexed versus placebo in patients whose disease has not progressed after 4 cycles of pemetrexed plus cisplatin. The primary endpoint is PFS, with a planned enrollment of more than 900 patients.

Promising results have been reported from a phase II study that not only introduced pemetrexed front-line (pemetrexed plus carboplatin plus bevacizumab) in patients who were eligible for bevacizumab, but also featured pemetrexed plus bevacizumab as first-line maintenance therapy.²² At a median follow-up of 13 months, the ORR was 55%, the median PFS was

TABLE 6

JMEN trial³⁸: outcomes with pemetrexed as first-line maintenance therapy after standard platinum-based doublet chemotherapy, analyzed according to tumor histology^a

Histology group	Median overall survival, months			Median progression-free survival, months		
	Pemetrexed	Placebo	P value (HR)	Pemetrexed	Placebo	P value (HR)
Nonsquamous (n = 481)	15.5	10.3	0.002 (0.70)	4.4	1.8	<0.00001 (0.47)
Adenocarcinoma (n = 329)	16.8	11.5	0.006 (0.73)	4.6	2.7	<0.00001 (0.51)
Large cell (n = 20)	8.4	7.9	0.964 (0.98)	4.5	1.5	0.104 (0.40)
Other (n = 113)	11.3	7.7	0.025 (0.61)	4.1	1.6	0.0002 (0.44)
Squamous (n = 182)	9.9	10.8	0.678 (1.07)	2.4	2.5	0.896 (1.03)

HR = hazard ratio

^aThere was a statistically significant treatment-by-histology interaction for both overall survival ($P = 0.33$) and progression-free survival ($P = 0.036$).

TABLE 7

Phase III studies of maintenance therapy with EGFR tyrosine kinase inhibitors^{19,39,44,46,47}

Trial	Treatment comparison	Progression-free survival (ITT)		Overall survival (ITT)	
		HR (95% CI)	P value	HR (95% CI)	P value
SATURN ³⁹	Erlotinib (n = 438) Placebo (n = 451)	0.71 (0.62, 0.82)	<0.0001	0.81 (0.70, 0.95)	0.009
ATLAS ^{19,46}	Bevacizumab + erlotinib (n = 370) Bevacizumab + placebo (n = 373)	0.72 (0.59, 0.88)	0.0012	0.92 (0.70, 1.21)	0.56
IFCT-GFPC 0502 ⁴⁴	Erlotinib (n = 155) Observation (n = 155)	0.82 (0.73, 0.93)	0.002	0.91 (0.80, 1.04)	NS ^a
EORTC 08021 ⁴⁷	Gefitinib (n = 86) Observation (n = 87)	0.61 (0.45, 0.83)	0.0015	0.83 (0.60, 1.15)	0.2

EGFR = epidermal growth factor receptor; ITT = intent-to-treat population; HR = hazard ratio; CI = confidence interval; NS = not significant

Data highlighted in color showed a significant difference between the two arms of the study.

^aSurvival data are premature as of October 2010.

9.8 months, and the median OS was 14.1 months.

The ongoing PointBreak trial⁴² not only compares pemetrexed versus paclitaxel for front-line treatment in bevacizumab-eligible patients (pemetrexed/carboplatin/bevacizumab vs paclitaxel/carboplatin/bevacizumab) but also compares two different maintenance regimens (pemetrexed/bevacizumab vs bevacizumab) after 4 cycles of treatment. The ECOG 5508 trial,⁴² which recently opened, is also designed to compare different maintenance strategies; patients with nonsquamous NSCLC receive carboplatin/paclitaxel/bevacizumab for 4 cycles, and then patients without disease progression are randomized 1:1:1 to receive maintenance treatment with bevacizumab, pemetrexed, or the combination of bevacizumab plus pemetrexed. Accrual of nearly 1,300 patients is planned.

Gemcitabine maintenance has been evaluated in several randomized trials. A phase III trial conducted by the Central European Oncology Group compared continuation maintenance with gemcitabine versus best supportive care only in patients whose disease had stabilized or responded after initial treatment with cisplatin plus gemcitabine.⁴³ The primary endpoint of improved PFS was reached ($P < 0.001$), with a median time to disease progression of

6.6 months for those receiving gemcitabine maintenance compared with 5.0 months with best supportive care alone ($P < 0.001$). Although there was a 2-month difference in OS (13.0 months and 11.0 months, respectively), this difference was not statistically significant.

More recently, results were reported from a French trial that looked at the same first-line platform regimen (cisplatin plus gemcitabine for 4 cycles) followed by randomization in the absence of disease progression to gemcitabine alone as continuation maintenance, erlotinib switch maintenance, or observation.⁴⁴ With respect to PFS, the primary endpoint, there was statistically significant improvement for both of the maintenance treatment arms compared with observation. For patients receiving gemcitabine continuation, the median PFS was 3.8 months (HR, 0.55; 95% CI, 0.43, 0.70; $P < 0.0001$). For those receiving erlotinib switch maintenance, the median PFS was 2.9 months (HR, 0.82; 95% CI, 0.73, 0.93; $P = 0.002$). There appears to be a trend toward improved OS in both maintenance therapy arms, but more mature data are needed to determine whether significance will be reached.

A third trial looked at continuation maintenance with gemcitabine versus best supportive care alone in a frailer, sicker population, in which

nearly two-thirds of patients were ranked PS 2 and 3.⁴⁵ Unfortunately, this trial was negative, demonstrating neither an OS nor PFS benefit. However, the results suggest that it is likely better to study maintenance strategies in healthier patient populations.

For first-line maintenance strategies with EGFR tyrosine kinase inhibitors, results are available from four randomized trials (Table 7).^{19,39,44,46,47} In each of these trials, in which switch maintenance therapy was compared with either an observation or a placebo control, a significant improvement in PFS was achieved with robust P values. Only one of these trials, however, has yielded an OS advantage.

In the SATURN study,³⁹ patients who had disease stabilization after receiving 4 cycles of standard first-line chemotherapy were randomized to receive either erlotinib maintenance or placebo. In the intent-to-treat population, patients receiving erlotinib maintenance had a significant improvement in median OS (12.0 months vs 11.0 months for placebo; HR, 0.81; 95% CI, 0.70, 0.95; $P = 0.009$).

In the ATLAS trial,^{19,46} which was similar in design to the SATURN trial but with the addition of bevacizumab, the PFS benefit of maintenance therapy did not translate into a survival benefit.

Case study #2

A 56-year-old white male former smoker (30 pack-years) presents with shortness of breath and cough; he has also experienced two episodes of hemoptysis. Physical exam shows a 1-cm right supraclavicular node and diminished breath sounds at the right base. Chest x-ray shows a right lower lobe mass with associated pleural effusion. A CT scan confirms this mass at 3.5 cm with a hilar, ipsilateral mediastinal right supraclavicular adenopathy, as well as right pleural effusion. Thoracentesis confirms adenocarcinoma, thyroid transcription factor-1 (TTF-1) positive, pointing toward a pulmonary source. Brain MRI is negative. Additional tumor testing is negative for EGFR mutations. The patient receives 6 cycles of carboplatin and paclitaxel, which he tolerates well, and his presenting systems resolve. Follow-up CT imaging shows resolution of pleural effusion, shrinkage of all nodes to less than 1 cm, and shrinkage of the primary mass to 1.5 cm.

What course would you follow at this point?

1. Observation
2. Continuation of carboplatin and paclitaxel beyond 6 cycles
3. Maintenance pemetrexed
4. Maintenance pemetrexed and bevacizumab
5. Maintenance taxane (docetaxel)
6. Maintenance erlotinib

Certainly, for this patient with adenocarcinoma, maintenance pemetrexed is an option, as is maintenance erlotinib. Bevacizumab is not approved specifically for maintenance, but it is an option as part of a continuation maintenance approach for those patients who received bevacizumab as part of their first-line regimen. In contrast, for patients with squamous cell carcinoma, the only FDA-approved maintenance therapy is erlotinib. Also, one should consider introducing erlotinib maintenance in patients with an EGFR mutation who, for some reason, have not received erlotinib up front. Overall, given these choices and the relative persuasiveness of the clinical trial results, maintenance pemetrexed would be the favored treatment option for this patient.

Conclusion

First-line treatment of advanced NSCLC has evolved over the past decade and now features a more individualized approach. Tumor histology is certainly important, as it dictates therapeutic choices. The optimal chemotherapy will differ based on whether the patient has a diagnosis of squamous versus nonsquamous NSCLC. Therefore, adequate tumor biopsies are of paramount importance.

Also, genotypically directed first-line therapy rather than chemotherapy is now a reality for patients with an activating EGFR mutation. Both

the EGFR and the VEGF pathways have been validated clinically as important tumor pathways in NSCLC, and a variety of other biologically targeted therapies directed against other pathways are being developed for use in NSCLC.

Studies are also needed to distinguish which patients may benefit most from maintenance therapy and which patients can undergo a treatment break. Individualization of maintenance strategies may consider clinical factors, such as age, PS, presence of symptoms, disease burden, and molecular markers (eg, EGFR

mutation status), as well as whether the patient achieved an objective response or stable disease with first-line chemotherapy.

Clearly, future treatment strategies will need to effectively incorporate clinical characteristics and predictive and prognostic molecular markers to further optimize individualized therapy for patients diagnosed with advanced NSCLC.

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