Best Practices in Treatment Selection for Patients With Advanced NSCLC

Mark A. Socinski, MD, and Nathan A. Pennell, MD, PhD

Summary: Worldwide, lung cancer is the most prevalent form of cancer, and its non–small-cell subtype constitutes up to 85% of cases. Overall, lung cancer is the most common cause of cancer-related death in the United States for both sexes, and its 5-year survival rate is 17%. It is a heterogeneous disease characterized by a variety of biomarkers and differing histologies. Non–small-cell lung cancer may be squamous or nonsquamous in nature and fueled by a number of oncodrivers. Obtaining sufficient tissue during biopsy to perform thorough biomarker testing is a challenge but essential for the modern, targeted therapeutic environment. Although platinum-based doublets still play a major role in first-line treatment, novel therapeutic agents targeting BRAF, EGFR, ALK, and ROS1, as well as agents targeting the T790M mutation, may offer options for patients whose disease fails to respond to initial therapy or relapses following an initial response. The emergence of immunotherapy as second-line standard therapy has changed the treatment paradigm. Some patients will have more favorable outcomes in the first-line setting with immunotherapy. However, managing lung cancer has become more complex than it was 15 years ago when the challenge of treatment was seen as being only binary, ie, small-cell vs non–small-cell disease.

Introduction
Non–small-cell lung cancer (NSCLC) represents a heterogeneous group of malignancies that constitutes 80% to 85% of lung cancers.1 Adenocarcinoma is the most common subtype of NSCLC and accounts for nearly 50% of cases.1 Worldwide, lung cancer represents the most common type of cancer: 1.8 million new cases of lung cancer were diagnosed in 2012 alone, and it is estimated to be responsible for 1 in 5 cancer-related deaths each year.2 It remains the most common cancer in men.2

Death rates from lung cancer in the United States have declined by 38% in men since 1990 and by 12% in women since 2002, primarily due to the decrease in smoking prevalence.3 Nonetheless, lung cancer remains the second most common cancer in both men and women in the United States, with 117,920 and 106,470 estimated new cases diagnosed in men and women, respectively, in 2016.3 Lung cancer is the leading cause of cancer-related death in the United States, with an estimated 85,920 deaths occurring in men and 72,160 deaths among women.4 This is partly because 16% of lung cancers are diagnosed at a localized stage when the 5-year survival rate is 55%; however, the overall 1- and 5-year survival rates for lung cancer are 44% and 17%, respectively.3
The following report presents highlights from a roundtable discussion between 2 leading medical oncology experts in NSCLC, Mark A. Socinski, MD, and Nathan A. Pennell, MD, PhD. The panel members share insights into the validity and clinical implications of a variety of NSCLC biomarkers, first- and second-line therapies for NSCLC of squamous or nonsquamous origin, and promising novel therapies on the horizon. Case studies are used to demonstrate selected therapeutic strategies in real-world clinical scenarios.

Scope of the Problem
Dr Pennell: Lung cancer is the second most common cancer in both men and women in the United States, but more Americans die of lung cancer than the next 4 most common cancers combined.1 Despite the fact that death rates have been dropping in men for sometime and, more recently, in women, it is still far and away the most important cancer from a morbidity and mortality perspective in the United States and worldwide.2,3 Despite excitement over treatment advances and the onset of screening in lung cancer, the 5-year survival rate remains at 18%.4,5

Dr Socinski: I might also mention here that, in comparison with breast cancer, we have a different stage demographic. At the time of diagnosis, most patients with lung cancer present with stage III/IV disease, whereas, because of awareness and screening, most patients with breast cancer present with stage I/II disease.4 Right out of the gate, we are disadvantaged with regard to long-term survival. Stage IV disease is treatable but not curable; with stage III disease, even though we approach it in some subset as curative, the majority of patients are not cured.5

Dr Pennell: It is heartening that smoking rates in American adults overall have dropped below 20%.6 It will take several decades for this change in behavior to be reflected in falling death rates from lung cancer. While we finally have Centers for Medicare & Medicaid Services coverage for the screening of lung cancer in high-risk patients, the process has not yet been widely enough adopted for us to see any real impact on lung cancer–related deaths.

Dr Socinski: This need for tissue is particularly true for adenocarcinoma patients in whom the number of markers we are testing for seems to be increasing yearly. We are rapidly entering an era where immunotherapy will be the preferred first-line treatment for a subset of patients. But you select those patients based on a biomarker performed from core biopsy.7 Most of the decision-making is made without consultation from a medical oncologist. Instead, pulmonologists, thoracic surgeons, and primary care physicians refer patients to interventional radiology. Those subspecialties may not know or have an appreciation of all the demands on tissues. The word needs to spread to these other disciplines.

Clinical Controversies and Challenges
Dr Socinski: One of the challenges we face in this population is getting an initial diagnosis and all that entails. Historically, we have approached this disease as a single entity. About 15 or 20 years ago the distinction we asked pathologists to make was to differentiate between small cell lung cancer and NSCLC, and that was pretty much it. We believed all NSCLCs were similar from a treatment perspective. This perspective changed with bevacizumab and pemetrexed when we decided it was important to distinguish between squamous and nonsquamous histologies. With the advent of modern molecular testing, obtaining adequate tissue for testing can be a challenge in the individual patient, particularly as the initial specimen on biopsy is often acquired before the patient sees an oncologist.

Dr Pennell: I completely agree. The biggest challenge is obtaining sufficient tissue and having enough institutional expertise in the pathology department where the biopsy is performed as well as good communication with those performing the biopsy. Going forward, nonsquamous NSCLC patients will need to have a fairly broad panel of molecular tests performed. This requires far more extensive testing, which represents a fairly high burden of need for sufficient tissue.7 Now we may even be talking about biomarkers such as programmed death ligand 1 (PD-L1). Meanwhile, a large number of individuals are diagnosed based on a brushing from bronchoscopy with a few cells and that is all you get. In many of these patients, it is fairly high risk to obtain tissue. This consideration is an issue I think does not receive nearly enough attention.8

Dr Socinski: This need for tissue is particularly true for adenocarcinoma patients in whom the number of markers we are testing for seems to be increasing yearly. We are rapidly entering an era where immunotherapy will be the preferred first-line treatment for a subset of patients. But you select those patients based on a biomarker performed from core biopsy.7 Most of the decision-making is made without consultation from a medical oncologist. Instead, pulmonologists, thoracic surgeons, and primary care physicians refer patients to interventional radiology. Those subspecialties may not know or have an appreciation of all the demands on tissues. The word needs to spread to these other disciplines.

Therapeutic Targets
What would you say is the standard of care today for the minimal number of genotypes that we should be testing?

Dr Pennell: We have consensus guidelines from the International Association for the Study of Lung Cancer and the College of American Pathologists that have recommended for years that every nonsquamous NSCLC or adenocarcinoma or suspected adenocarcinoma be tested for EGFR mutations as well as for ALK rearrangements.9

However, most of us recognize that current guidelines require updating. At a minimum, I think that EGFR mutations and ALK and ROS1 rearrangements should be tested for in every newly diagnosed patient with adenocarcinoma or select squamous cell patients with a minimal smoking history.9,10 However, I would argue that there are a number of other markers that
should routinely be tested for if those 3 are negative. At the most recent annual meeting of the American Society of Clinical Oncology (ASCO), mature data on the combination of the B-raf proto-oncogene inhibitor dabrafenib and the mitogen-activated protein kinase (MEK) inhibitor trametinib were presented that might argue for the testing of those biomarkers and the BRAFV600E mutation in NSCLC.10

Dr Socinski: What about the clinical significance of the data presented on MET alteration at ASCO?

Dr Pennell: I think MET is the next big target. Now that we have recognized the phenomenon of these driver mutations and have demonstrated, even in relatively small numbers of patients, that agents targeting these mutations lead to high response rates with durable disease control, I do not think we need to wait for a major phase 3 trial to start saying that these are genetic rearrangements for which we need to start testing.

In the past few years, we have also identified the exon 14–skipping mutation, which appears to be a real driver mutation present in about 4% of adenocarcinomas.11 These mutations are probably as common as ALK rearrangements and seem to respond to MET inhibitors like crizotinib, which is typically used for ALK and ROS1 rearrangements but also works well as a MET inhibitor.12

Dr Socinski: I agree. We have evidence in patients with EGFR mutations and ALK-positive disease that targeted oral tyrosine kinase inhibitors (TKIs) are superior to chemotherapy on the basis of their rate of progression-free survival (PFS) and their toxicity profile.13-15 We also have a drug approved by the US Food and Drug Administration (FDA) for ROS1 rearrangements — crizotinib — yet we do not have any randomized data.16 However, I would not be in favor of conducting a 300- to 400-patient randomized trial of dabrafenib plus trametinib vs a platinum-based doublet as the control arm to prove that targeting the oncogenic driver is better than nonspecific cytotoxic chemotherapy.

Dr Pennell: I agree. When you have 2 small phase 2 trials and you show a response rate of 70% and PFS in the 10- to 12-month range, which is basically double what we see with chemotherapy, and there is a favorable toxicity profile and enough experience with safety to know that it is something reasonable for patients, then I think the FDA needs to be more flexible in how it is conducting approvals (Table 1).17,18 It can be very challenging to conduct randomized trials targeting a mutation present in 1% to 2% of lung-cancer patients.10 Furthermore, it is not ethical to randomly assign a patient to chemotherapy when one knows that there are other agents that are active against in their disease.

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**Table 1. — Select Adverse Events Associated With Crizotinib or Dabrafenib Plus Trametinib**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Crizotinib, %</th>
<th>Dabrafenib + Trametinib, %</th>
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<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
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<tr>
<td>Gastrointestinal</td>
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<tr>
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</tr>
<tr>
<td>Nausea</td>
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<td>0</td>
</tr>
<tr>
<td>Constipation</td>
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<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
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<td>2</td>
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<tr>
<td>Dysgeusia</td>
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<td>0</td>
</tr>
<tr>
<td>Dyspepsia/upper abdominal pain</td>
<td>10</td>
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<td>Decreased appetite</td>
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<tr>
<td>Hematological</td>
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<tr>
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<td>—</td>
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<tr>
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Data from references 17 and 18.
enocarcinoma patients.\textsuperscript{19-21} I do not know why there has not been more attention given to clinical trials in this population, because these mutations seem to be as common as others, and there are a lot of agents available that target ERBB2. Some European cohorts have evaluated broad genetic testing and off-label use of anti-ERBB2 agents, suggesting that there can be activity with both TKIs and a monoclonal antibody like trastuzumab.\textsuperscript{20,22}

**Dr Socinski:** I would not say ERBB2 needs routine testing, but, if it is identified, then I would probably reserve any off-label use until patients have exhausted proven therapies. What role does KRAS have currently?

**Dr Pennell:** We routinely test for KRAS, but it is a bit of a holdover from our initial approach where we tested for EGFR, ALK, and KRAS. If KRAS tests positive — which it does in about 15% to 25% of adenocarcinoma patients — we do not feel it is necessary to test for other potential drivers.\textsuperscript{23} I think it is still useful in that setting. It is also useful to know in terms of selecting patients for clinical trials. However, in terms of determining treatment outside of a clinical trial, testing for KRAS mutations is not really all that helpful, other than you no longer have to worry about looking for other potential drivers.

**Dr Socinski:** What about RET alterations? We have a number of small phase 2 trials suggesting that various ret proto-oncogene (RET) inhibitors have activity.\textsuperscript{24,25} However, the level of activity in these alterations does not seem to be as impressive as the other markers we have discussed. At the ASCO annual meeting, Reckamp et al.\textsuperscript{26} presented data on targeting RET alterations: response rates were 20% to 40% and the durability of response was not highly impressive. I might place RET in the same category as ERBB2.

**Dr Pennell:** I think we have a little more data with various available agents for RET than ERBB2.\textsuperscript{27-31} However, the data are disappointing.\textsuperscript{27,30-33} It is a proven driver oncogene, but I agree with you. I would not treat someone with a RET fusion with a RET inhibitor as first-line therapy.

**Dr Socinski:** As for DDR2, the data we have are very immature; however, this is a potentially attractive target in patients with squamous histology.\textsuperscript{34,35}

**Dr Pennell:** I think we all want to find targets that we can exploit in squamous cell carcinoma (SCC), and amplifications and mutations of DDR2 or FGFR1 occur in a significant percentage of patients with SCC.\textsuperscript{34-36} However, the actionability of those targets and the clinical activity of the agents that we have targeting them are unproven at this point.

I do think we need to support the LUNG-MAP protocol to try to put squamous-cell patients on some of these targeted agents so that we can actually get a better idea of how active they are.\textsuperscript{37} I know that DDR2 is also part of the NCI-MATCH study.\textsuperscript{38}

**Practical Considerations in Biomarker Testing**

**Dr Socinski:** If I were advising a large community hospital in terms of testing practices, I would suggest being as cost effective as possible and identifying those patients who would receive a major benefit from targeted therapy. I would test for EGFR, ALK, MET amplification, exon 14 mutation, ROS1, BRAF, and KRAS. At the University of Pittsburgh Medical Center, 31% of the population of adenocarcinomas had a KRAS alteration.\textsuperscript{39} As for other drivers beyond those I just mentioned, you are in the 1% to 2% range, and, for many of the other alterations, we do not yet have robust clinical data that indicate a targeted agent has an impact.\textsuperscript{40}

**Dr Pennell:** I want to address the cost effectiveness of testing. In the past we would test for EGFR mutations and ALK rearrangements, and we now have ROS1-approved agents. Although getting insurance coverage is not difficult for the majority of those individual tests, we now have so many tests that really should be considered standard of care that it is much more cost effective to do a single broad test.\textsuperscript{41} It conserves tissue, gives you information faster, and it is cheaper to pay for 1 test than it is to pay for 6 individual tests.

**Dr Socinski:** Yes, I agree. Panels and next-generation sequencing strategies are probably going to end up being the most cost effective. One of the issues I struggle with is just how much information is necessary. Sometimes it is confusing to figure out the impact of testing in an individual patient. We do not know if all of the targets identified are valid.

**Dr Pennell:** Extremely broad testing of hundreds of potential genes does not have much clinical validity. I think guided molecular testing for proven targets makes sense. Broader testing from a purely research standpoint makes sense; however, I would not recommend broader testing be routinely performed for patients who have no intention of enrolling in a clinical trial.

**Case Study: Treatment of Stage IVb Nonsquamous Disease**

A 65-year-old man presents with a good Eastern Cooperative Oncology Group (ECOG) performance status (PS; 0–1 and no comorbidities) and a diagnosis of stage IVb NSCLC. The patient is tested for all common oncogenic biomarkers, including EGFR, ALK, ROS1, MEK, MET, BRAF V600E, and KRAS, but no oncogenic
driver is identified. Histological testing reveals adenocarcinoma.

This individual is a healthy patient eligible for anything that we might want to use. An upfront, targeted agent would not be appropriate outside of a clinical trial for this patient, so platinum-combination chemotherapy would be the standard of care.

There are 2 established regimens in this setting. A carboplatin and paclitaxel doublet with the anti–vascular endothelial growth factor antibody bevacizumab has been established for more than 10 years now and is effective as first-line therapy.\textsuperscript{42,43} A second regimen that is becoming more common these days is the combination of a platinum agent with pemetrexed. There are head-to-head data from a phase 3 trial showing that, in the nonsquamous NSCLC setting, this regimen is more effective and tolerable than a platinum doublet-containing regimen.\textsuperscript{44-46} I am not a fan of adding bevacizumab to pemetrexed. We do not have any randomized evidence suggesting that adding bevacizumab results in any meaningful clinical benefit. However, there are adequate safety data on that combination and it is commonly used.\textsuperscript{47-49} My personal preference is to use carboplatin and pemetrexed in an otherwise healthy patient with adenocarcinoma who has no comorbidities.

**Dr Socinski:** The PointBreak trial showed us that, whether you use bevacizumab with carboplatin and paclitaxel or carboplatin and pemetrexed, the outcomes in terms of response and survival are equivalent.\textsuperscript{45,46} It makes me uncomfortable that we are accepting that a 2-drug regimen is as good as the 3-drug regimen. The PRONOUNCE trial did not demonstrate the superiority of carboplatin and pemetrexed followed by pemetrexed maintenance vs carboplatin and paclitaxel plus bevacizumab followed by bevacizumab maintenance.\textsuperscript{49} However, I do not see that as a definitive phase 3 trial.

My tendency is to try to figure out what is the best doublet for the patient. If carboplatin with pemetrexed is a reasonable choice for the patient — and there are some clear advantages for pemetrexed\textsuperscript{51} — I would use that agent. However, I do not want to portray pemetrexed as being without toxicity. Common adverse events associated with pemetrexed include fatigue, nausea, and anorexia.\textsuperscript{52} When combined with a platinum agent, vomiting, neutropenia, leukopenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation are common.\textsuperscript{52} The next question is: Am I going to add a biologic agent to it? There are phase 3 data from large trials suggesting that, whether you add bevacizumab to pemetrexed or a taxane, the outcomes are equivalent.\textsuperscript{45}

**Dr Pennell:** If you were using carboplatin and a taxane with bevacizumab as your choice for this patient, then it sounds as if you would be in favor of maintaining therapy if a response was evident.

**Dr Socinski:** Yes, I agree. If there were contraindications to bevacizumab and the patient was receiving carboplatin and pemetrexed and was either stable or responding and tolerating therapy well, would you continue with pemetrexed maintenance?
**Dr Pennell:** Yes, that is the standard of care now. We have a couple of good phase 3 trials supporting a survival benefit through either continuation or a switch to maintenance with pemetrexed if you have a non-bevacizumab regimen for first-line therapy.

**Case Study: Treatment of Stage IVb Squamous Disease**

A 65-year-old man presents with a good ECOG PS (0–1 and no comorbidities) and a diagnosis of stage IVb NSCLC. The patient is tested for all common oncogenic biomarkers, including EGFR, ALK, ROS1, MEK, MET, BRAF V600E, and KRAS, but no oncogenic driver is identified. Histological testing reveals SCC.

**Dr Socinski:** I think that the standard of care is again platinum-based doublet therapy. The choices really reside between platinum-based therapy plus a taxane, including paclitaxel, docetaxel, and nab-paclitaxel, and a gemcitabine-containing regimen. However, I think the evidence suggests that taxane-based therapy is a better approach than gemcitabine therapy.

Gemcitabine has some side-effect advantages that the taxanes do not have. When gemcitabine is used as a single agent, the most common adverse effects are nausea and vomiting, anemia, hepatic transaminitis, neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and peripheral edema.

In elderly patients receiving biweekly carboplatin plus gemcitabine as first-line therapy for advanced squamous NSCLC, grade 3/4 neutropenia occurred in 12.3% of patients, grade 3/4 thrombocytopenia occurred in 7.1%, and grade 2/3 fatigue occurred in 17.5%.

For maintenance therapy, we have fewer options. We do not use bevacizumab or pemetrexed in patients with squamous histology; however, we do have some evidence for maintenance gemcitabine or maintenance taxane therapy. Nonetheless, there is no clear-cut advantage in that setting, and, in squamous NSCLC, I generally do not use maintenance therapy. I watch patients closely, and then I think about second-line therapy at the time of disease progression.

We do have data sets in the squamous population that we should discuss. There is a suggestion relative to standard taxane therapy that nab-paclitaxel has higher response rates. Response rates are important in the lung-cancer setting as they correlate with symptom relief. If you shrink the tumor, the patient feels better.

**Dr Pennell:** From the standpoint of SCC, I think that the choice is clearly one of the taxanes — paclitaxel or nab-paclitaxel — vs gemcitabine. I choose based on which adverse-event profile fits the patient best. Treatment with nab-paclitaxel plus carboplatin is associated with a higher incidence of neutropenia and leukocytopenia compared with gemcitabine plus carboplatin. In patients treated with nab-paclitaxel as monotherapy, anemia occurred in 38%, leukopenia in 48%, neutropenia in 38%, thrombocytopenia in 11%, and febrile neutropenia in 10%. Nonhematological adverse events include alopecia (67%), fatigue (58%), sensory neuropathy (59%), anorexia (29%), nausea (36%), myalgia (19%), and arthralgia (26%). For patients who do not want to lose their hair, typically I would select gemcitabine; for patients who live far away and would rather receive treatment every 21 days, I think paclitaxel makes more sense. I am not sure if I buy into nab-paclitaxel being better because of the response rate being somewhat higher. However, I am a little more impressed with the data in the elderly population using nab-paclitaxel (Fig).

![Fig A–B. — Kaplan–Meier curve for (A) PFS and (B) OS rates according to cycles of nab-paclitaxel monotherapy in elderly patients with relapsed squamous NSCLC. CI = confidence interval, OS = overall survival, PFS = progression-free survival. Reprinted with permission of Dove Medical Press, from A retrospective analysis of safety and efficacy of weekly nab-paclitaxel as second-line chemotherapy in elderly patients with advanced squamous non-small-cell lung carcinoma, Jin F, Zhu H, Shi F, et al., 2016;11, 2016; permission conveyed through Copyright Clearance Center, Inc.](image-url)
Dr Socinski: Yes, we have to remember that, even though a superior overall response to nab-paclitaxel was demonstrated, this finding did not translate into differences in PFS or OS. However, I do consider nab-paclitaxel as the treatment of choice in a patient with heavy-disease burden who is very symptomatic, because, if you have a higher likelihood of shrinking the tumor, then that patient is probably experiencing greater clinical benefit. He or she may live better, though not necessarily longer in that setting.

Dr Pennell: We need to remember that squamous NSCLC patients are often older, and they often have more comorbidities than other NSCLC patients. Comorbidity is a big factor in these patients. I often use gemcitabine for that reason, but I also use nab-paclitaxel in some patients because it is associated with less neuropathy and you see patients more often so you can monitor them. It also has the advantage of not requiring the use of premedication with steroids. Unfortunately, we do have to think about cost as well.

Dr Socinski: Nab-paclitaxel is FDA approved and has a weekly schedule. However, it should not be administered to patients with a baseline neutrophil count of less than 1,500 cells/mm³, and it is recommended that peripheral blood cell counts be monitored frequently in those receiving the agent. Some elderly patients like coming weekly because they get more attention, and they can deal with their problems prospectively, while others have geographical issues that make weekly visits impossible. These needs are why you have to individualize treatments.

The role of necitumumab in squamous NSCLC has to be considered as well. The SQUIRE trial was a large, phase 3 trial of gemcitabine plus cisplatin with or without necitumumab as first-line therapy in patients with stage IV squamous cell NSCLC. The trial demonstrated an OS advantage, which led to its approval by the FDA and, although no significant difference in response rate was seen, a modest benefit in PFS was observed. The primary toxicities of necitumumab include skin rash, gastrointestinal toxicity, and hypomagnesemia.

Dr Pennell: LUX-Lung 8 was a trial of afatinib vs erlotinib in SCC of the lung. It was a phase 3 trial that showed longer PFS and OS rates, as well as a slightly higher response rate for afatinib in patients with stage IIIb/IV squamous NSCLC who had progressed after at least 4 cycles of platinum-based chemotherapy. However, use of EGFR TKIs has fallen out of favor in EGF wild-type patients due to marginal activity.

Dr Socinski: Yes, afatinib is now indicated for metastatic squamous NSCLC that has progressed after platinum-based chemotherapy.

Case Study: Second-Line Therapy

A 65-year-old man presents with a good ECOG PS (0–1 and no comorbidities) and a diagnosis of stage IVb NSCLC. Second-line therapy is indicated. A lot has changed in the past year or so and we have a new standard. We have the results of the CheckMate

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)</th>
<th>P Value</th>
<th>Median Survival, mo</th>
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<tbody>
<tr>
<td>Overall</td>
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<tr>
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CI = confidence interval, HR = hazard ratio, IHC = immunohistochemistry, NSCLC = non–small-cell lung cancer. Data from reference 69.
017 trial of squamous NSCLC comparing nivolumab with docetaxel; it showed a 50% improvement in median survival and a doubling of the response rate. This study was an impressive trial that really changed the second-line standard. We also saw that same effect — although to a lesser degree — in the nonsquamous NSCLC CheckMate 057 trial, which led to nivolumab receiving an indication for the treatment of metastatic NSCLC in patients who have progressed on or after platinum-based chemotherapy. KEYNOTE-010 had a similar design to the 2 CheckMate trials, with docetaxel as the control arm compared with pembrolizumab. These trial results have radically transformed our second-line platform.

**Dr Pennell:** Within a month or two of the approval of nivolumab for squamous cell disease, we were routinely using that in everyone as second-line therapy over chemotherapy. Then we began using nivolumab in adenocarcinoma and nonsquamous disease almost as rapidly.

**Dr Socinski:** Nivolumab established itself as the standard not only because it was the first to be approved, but also due to the fact that it was not linked to a biomarker. By contrast, pembrolizumab approval was linked to the biomarker PD-L1.

**Dr Pennell:** It is important to recognize the different populations involved in the CheckMate and KEYNOTE trials. Pembrolizumab was only approved in patients who were positive for the PD-L1 biomarker, as these individuals were the only patients enrolled in the trial to be randomized to pembrolizumab vs chemotherapy. By contrast, in the nivolumab trials, the investigators took all comers, and PD-L1 was used to stratify response based on expression. The overall intent-to-treat population had a big survival benefit without relying on being PD-L1 positive. There is a difference in efficacy, especially in nonsquamous patients treated with nivolumab, where higher levels of PD-L1 expression do infer a greater survival benefit and a higher response rate compared with docetaxel. However, even patients with no PD-L1 expression have OS and response rates comparable with docetaxel.

For second-line patients, I would not recommend routine testing of PD-L1 because the only purpose of testing would be to select an alternate treatment. There really is no alternate treatment that would be a better choice.

**Dr Socinski:** I agree, but I think that PD-L1 is going to play a very important role in the first-line setting. What is your take on the different adverse-event profiles of the immunotherapy agents?

**Dr Pennell:** The majority of patients have very few adverse events — maybe some fatigue, aches, and pains. However, these are often associated with having lung cancer. Nonetheless, up to 10% of patients do have serious adverse events, which are usually related to autoimmune effects secondary to these agents. With nivolumab and pembrolizumab, we do not see nearly the level of autoimmune-related adverse events seen with the anti-cytotoxic T-lymphocyte-associated antigen 4 agents such as ipilimumab. Severe to fatal immune-mediated adverse reactions have been reported in up to 41% of patients, including 16% who experienced enterocolitis, 11% who experienced hepatitis, 4% dermatitis, 2% neuropathy, and 7% hypopituitarism. Immune-mediated pneumonitis, meningitis, myocarditis, and pericarditis have also been reported.

However, the adverse events of PD-1 inhibitors can still be serious. With nivolumab, immune-mediated pneumonitis occurred in 3.4% of NSCLC patients, immune-mediated colitis occurred in 2.4%, hepatitis occurred in 0.3%, adrenal insufficiency in 0.3%, hypothyroidism in 7.0%, hyperthyroidism in 1.4%, renal dysfunction in 0.3%, and immune-mediated rash in 6.0%. Other immune-related adverse events associated with nivolumab include encephalitis, pancreatitis, uveitis, iritis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain–Barre syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, and sarcoidosis. Pembrolizumab therapy has been associated with pneumonitis (3.5%), colitis (0.7%), hyperthyroidism (1.8%), hypothyroidism (6.9%), hypophysitis (0.2%), and type 1 diabetes mellitus (0.1%). Other immune-mediated adverse events associated with pembrolizumab include hepatitis, rash, vasculitis, nephritis, hemolytic anemia, serum sickness, and myasthenia gravis. Patients need to be monitored for events such as autoimmune colitis, hepatitis, and thyroiditis resulting in hypothyroidism, but this does not necessarily require altering treatment other than replacing thyroid hormones. However, everyone worries about pneumonitis, which occurs in 4% of 5% of patients. It is common enough that you need to watch for it and be ready to treat it, but it is still relatively uncommon.

**Dr Socinski:** It really is a small minority of patients — typically less than 5% who experience the more serious immune-related events. However, once we start using these agents routinely as first-line therapy — agents that potentially may be used for years in some patients who are receiving benefit — then the awareness of these toxicities will increase. It is going to be important to understand and be able to treat these immune-related toxicities.

**Dr Pennell:** As for first-line therapy, KEYNOTE 024 explored pembrolizumab vs platinum-based doublet chemotherapy in treatment-naive patients with very
high-level PD-L1 expression. A press release stated that pembrolizumab was superior to chemotherapy for both the primary end point of PFS and the secondary end point of OS. Based on these results, an independent data monitoring committee has recommended that the trial be stopped and patients receiving chemotherapy be offered the opportunity to receive pembrolizumab. Top-line results from CheckMate 026, a phase 3 study of nivolumab vs platinum-based doublet chemotherapy in treatment-naive patients with advanced NSCLC that also expressed PD-L1 but at a lower cutoff level, were also released. However, as monotherapy, nivolumab did not meet its primary end point of improved PFS when compared with platinum-based doublet chemotherapy in this patient population. Results from both trials will be presented at the annual congress of the European Society for Medical Oncology in early October 2016, but, at the time of press, these data were not yet available.

I think most of us expected that immunotherapeutic agents were eventually going to have a role as first-line therapy. We are going to see the need to routinely test for biomarkers to identify patients who would benefit from these drugs as initial therapy. We also have ongoing trials in patients looking at levels of PD-L1 expression, and combination trials of chemotherapy and immune checkpoint inhibitors as well as immune checkpoint inhibitor maintenance therapy following chemotherapy (NCT02758314, NCT02382406, NCT02564380). Testing for the biomarker is going to become part of our standard of care very soon.

Case Study: Treatment of EGFR Mutation-Positive Disease

A 65-year-old man presents with a good ECOG PS (0–1 and no comorbidities) and a diagnosis of stage IVb NSCLC. Adenocarcinoma is identified as well as a sensitizing EGFR mutation.

Everyone with NSCLC should be tested first line for EGFR. If you are identifying an activating EGFR mutation, then in most cases this will be an exon 19 deletion mutation or an exon 21 point mutation. We have excellent randomized phase 3 data from multiple trials suggesting that TKIs (eg, gefitinib, erlotinib, afatinib) are all superior to chemotherapy with probably twice the response rate, twice the PFS, and a more favorable tolerability profile. The phase 2 LUX-Lung 7 trial evaluated gefitinib vs afatinib and observed longer PFS with afatinib and a slightly higher response rate. There are also data from the LUX-Lung 3 and 6 trials suggesting that patients with an exon 19 deletion potentially derived not only a PFS benefit but also an OS benefit with afatinib.

I think that, in a healthy patient in whom there is no concern about skin toxicity or other potential toxicities, afatinib is a slightly more effective choice for first-line therapy. However, afatinib does have a higher toxicity rate than the first-generation TKIs. Diarrhea occurred in 96% of patients receiving afatinib with 15% of cases being grade 3 in severity, whereas diarrhea occurred in 62% of patients receiving erlotinib, with 5% of cases being grade 3/4 in severity (Table 3). In 6.1% of patients receiving afatinib, renal impairment occurred as a result of diarrhea.

For many of my frail elderly patients, I still use erlotinib as first-line therapy. By contrast, afatinib would probably be my first-line choice for a healthy young person.

Table 3. — Select Adverse Events (All Grades) in Patients Receiving Afatinib, Erlotinib, or Gefitinib

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Afatinib</th>
<th>Erlotinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>96.0</td>
<td>62.0</td>
<td>34.9</td>
</tr>
<tr>
<td>Skin reactions</td>
<td>90.0</td>
<td>85.0</td>
<td>57.9</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>71.0</td>
<td>17.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Nail disorder</td>
<td>58.0</td>
<td>14.0</td>
<td>7.9</td>
</tr>
<tr>
<td>Anorexia/decreased appetite</td>
<td>29.0</td>
<td>52.0</td>
<td>19.7</td>
</tr>
<tr>
<td>Pruritus/dry skin</td>
<td>21.0</td>
<td>16.0–21.0</td>
<td>—</td>
</tr>
<tr>
<td>Vascular disorder/hemorrhage</td>
<td>17.0</td>
<td>—</td>
<td>4.3</td>
</tr>
<tr>
<td>Cystitis</td>
<td>13.0</td>
<td>—</td>
<td>1.1</td>
</tr>
<tr>
<td>Cheilitis</td>
<td>12.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>12.0</td>
<td>36.0</td>
<td>8.7</td>
</tr>
<tr>
<td>Ocular disorder</td>
<td>11.8</td>
<td>17.8</td>
<td>7.0</td>
</tr>
<tr>
<td>Hepatic disorder</td>
<td>10.1</td>
<td>—</td>
<td>22.0</td>
</tr>
<tr>
<td>Renal failure</td>
<td>6.1</td>
<td>0.5</td>
<td>—</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>1.5</td>
<td>1.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Bullous/exfoliative skin disorders</td>
<td>0.2</td>
<td>1.2</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Alopecia</td>
<td>—</td>
<td>—</td>
<td>4.7</td>
</tr>
<tr>
<td>Asthenia</td>
<td>—</td>
<td>17.7</td>
<td>—</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>—</td>
<td>0.6</td>
<td>—</td>
</tr>
<tr>
<td>Cough</td>
<td>—</td>
<td>48.0</td>
<td>—</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>—</td>
<td>45.0</td>
<td>—</td>
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<tr>
<td>Gastrointestinal perforation</td>
<td>—</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>—</td>
<td>0.4</td>
<td>—</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>—</td>
<td>—</td>
<td>0.2</td>
</tr>
<tr>
<td>Myocardial infarction/ischemia</td>
<td>—</td>
<td>0.2</td>
<td>—</td>
</tr>
<tr>
<td>Nausea</td>
<td>—</td>
<td>33.0</td>
<td>17.8</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>—</td>
<td>—</td>
<td>0.1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>—</td>
<td>—</td>
<td>13.8</td>
</tr>
</tbody>
</table>

Data from references 75, 101, and 102.
**Dr Socinski:** What are your expectations when you start a TKI? What do you tell your patients to expect in terms of response and PFS? Then, what do you do when they progress?

**Dr Pennell:** Well, the good thing about these TKIs and EGFR mutations is that patients start to see improvements in symptoms within days to weeks. I usually bring them back 3 to 4 weeks after they start treatment because that is when you can expect to see the skin rash emerge and be ready to jump in with antibiotics (eg, doxycycline, minocycline) or topical agents to help them manage the skin toxicity. For most patients, supportive care for skin toxicity or diarrhea or a dose reduction can allow them to continue treatment. Patients live very active normal lives on these agents. The average or median time to progression is approximately 1 year.

Although I have patients who have been on EGFR TKIs for many years with disease control, inevitably their disease will progress. In the past, I would usually switch these patients to chemotherapy if they had previously received first-line treatment with a TKI. However, these days, we have another choice. For the 50% to 60% of patients who develop acquired resistance and progression on a first-line TKI, if you test them you may identify T790M, which is a gatekeeper mutation on exon 20 of EGFR. We have an agent that has been approved to treat this — osimertinib — which is very effective in patients with confirmed T790M. It requires testing, however, because the agent is only approved if patients are T790M positive. In addition, the data suggest that, if this mutation is not present, then osimertinib may not be effective and you may be better off switching to chemotherapy.

**Dr Socinski:** Testing upfront is standard. However, should the testing be performed on plasma, urine, or tissue?

**Dr Pennell:** Tissue is the gold standard; however, obtaining tissue for progression from all patients is difficult if not impossible. We have good evidence that the commercially available blood-based assays are quite sensitive and reliable. If the assay finding is negative for mutations, then you can perform a tissue biopsy. In June 2016, the FDA approved the EGFR mutation test v2, which is a blood-based companion diagnostic tool for erlotinib that includes T790M.

**Dr Socinski:** Assuming then that a patient is T790M negative, is standard chemotherapy the option you would recommend?

**Dr Pennell:** For most patients who have generalized symptomatic progression, I switch them to chemotherapy. In some patients, the progression can be relatively indolent, and you can watch them without changing treatment for awhile. If they are not symptomatic, then you do not need to rush to change treatment. In one-fifth of these patients, progression can be localized to maybe a single site or a few sites. We actually have a clinical trial testing stereotactic radiotherapy to areas where we have very limited focal progression.

We also have some pretty good biopsy data suggesting that not every metastasis develops acquired resistance at the same time, and that patients may sometimes remain on treatment for significantly longer if you ablate the areas that are progressing. In these cases, patients can remain on their first-line TKI. However, most patients who progress need to switch to something else. For me, stopping the TKI and moving on to chemotherapy is the choice for most patients.

**Dr Socinski:** I would like to talk about ALK-positive disease, which occurs in up to 5% of patients with NSCLC. In the first-line setting, we have randomized data suggesting that crizotinib is better than the best chemotherapy, which is pemetrexed plus a platinum-based agent. But, we now have more choices. Crizotinib was initially developed as a MET inhibitor, but it has ALK activity. Would you say that crizotinib is still your first-line choice, or are you tempted to use one of the other agents initially?

**Dr Pennell:** Crizotinib is typically my first-line choice for ALK-positive patients, but I go back and forth about this consideration. A Japanese phase 3 trial of alectinib vs crizotinib demonstrated a significantly prolonged PFS for alectinib. Alectinib is approved as second-line therapy in patients with locally advanced or metastatic ALK-positive NSCLC after failure of crizotinib. What has not been shown is that alectinib results in improved duration of disease control in patients who start on crizotinib, then switch to alectinib as second-line therapy at the time of progression. This strategy sequence is really what we consider the current standard of care. However, I would like to see a trial that examines the sequencing of the agents to determine which is better. I would not be surprised if alectinib becomes a reasonable standard first-line treatment option. For now, I still use crizotinib.

**Dr Socinski:** The second-generation TKIs (eg, alectinib, ceritinib, investigational agent brigatinib) have demonstrated favorable safety and efficacy profiles but with notable activity in the brain.

**Dr Pennell:** The clinical data suggest these second-generation agents penetrate the central nervous system. ALK-positive NSCLC patients commonly develop brain metastases. Crizotinib is not very ef-
effective in that setting.118 Some have suggested that more than one-half of patients with ALK-positive NSCLC develop brain metastases as the first sign of progression.119 If we can prevent or delay brain metastases, then that alone might be a good reason to use a more potent agent as first-line therapy.

**Dr Socinski:** Because we monitor the brain, frequently we find these lesions when they are relatively small and asymptomatic. TKI therapy can be a more effective alternative for these patients instead of going right to whole-brain or targeted radiotherapy.119 You may be able to delay treating the whole brain with the use of TKIs in this population.

I would also like to point out that the ALK-positive subset of patients seems to be very different than those with a EGFR mutation. Among patients with EGFR mutations, a dominant acquired resistant mutation, T790M, affects 50% to 60% of patients.119 The same phenomenon has not been observed in ALK-resistant patients. We have acquired mutations in up to 30% of patients, and 8 different mutations have been described.120-123 Furthermore, the resistance to ALK-TKIs involves both ALK- and non–ALK-mediated pathways.120

**Dr Pennell:** It does appear that brigatinib is effective against all of the demonstrated resistance mutations, at least in vitro.124 However, more than 50% of patients do not have an acquired secondary mutation as their mechanism of resistance.125 ALK-positive NSCLC presents a different picture than EGFR mutant-disease does.120-125

**Conclusions**

**Dr Socinski:** The management of advanced non–small-cell lung cancer has transitioned in the past decade with our increased understanding of the biology of the different subsets of patients. The emergence of immunotherapy — now our second-line standard and soon to become our first-line standard therapy — and the use of biomarkers in this setting are important developments of which clinicians should be aware. There will be a subset of patients who better respond to treatment in the first-line setting with immunotherapy. However, the complexity of the management of lung cancer has become exponentially greater than it was 10 or 15 years ago when we thought of the problem as small-cell vs non–small-cell disease. This evolution in how we manage the disease today puts a tremendous amount of pressure on our diagnostic colleagues to obtain adequate tissue for molecular testing.

We need new ideas for patients. Likewise, we need studies to examine the activity of chemotherapy following immunotherapy in patients with non–small-cell lung cancer. The fact that the number of therapeutic options has greatly expanded is a source of optimism; however, we must be thoughtful about how we approach our patients. We need to do our due diligence in molecular testing and we need to understand when to intervene with immunotherapy and what the benefits of that may be.

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