Message From the Course Director

Dear Colleague,

Thank you for joining us for this evening’s symposium.

The treatment landscape for non–small-cell lung cancer (NSCLC) continues to expand, and it is becoming increasingly more challenging to navigate the complex evidence and determine how new advances should be translated into practice. Treatment of patients with NSCLC should be individualized and based on the latest evidence; guidelines/expert consensus recommendations; relevant tumor-, patient-, and treatment-related factors; as well as patient needs and preferences. Effective collaboration and shared decision-making among healthcare providers, patients, and their family/caregivers is paramount in modern lung cancer care.

What does all of this mean for clinicians and patients with lung cancer? My colleagues and I answered this question at a live event held on June 5, 2016. We planned a stimulating, interactive learning session that integrated the expertise of some of the top lung cancer specialists with that of a lung cancer patient/advocate, providing multiple perspectives. We reviewed the latest data that should be considered in the management of both non-squamous and squamous NSCLC, including ALK- and EGFR-targeted therapies, other biologic options, cytotoxic agents, and of course, novel immune checkpoint blockade therapies. To help translate evidence into clinical practice, we also reviewed a series of case scenarios throughout the program. Several discussion forums were held to debate critical issues, controversies, as well as the practicalities of how to determine the best treatment for each patient at the right time. Our patient representative spoke on behalf of other lung cancer patients and their families/caregivers about their experiences, needs and expectations, how we can move towards more patient-centric lung cancer care, and what resources are available to help patients become well-informed participants in their care.

If you weren’t able to join us in person or via our live webcast, I encourage you to review this program through our onDemand activity.

Sincerely,

Mark A. Socinski, MD
Activity Description and Educational Objectives

This unique live learning session will convey practical guidance for how to effectively navigate the current lung cancer treatment landscape and collaboratively make shared decisions that are aligned with the latest evidence as well as each patient’s needs and preferences. Going beyond the standard didactic lectures, a panel of clinical experts and a patient voice representative will engage the audience in a stimulating discussion of the most up-to-date clinical data related to a range of treatment options (targeted agents, immunotherapies, chemotherapies) for NSCLC and implications for practice, all put within perspective with a framework of a series of real case scenarios debated throughout the symposium.

Upon completion of this activity, participants will be able to:
- Assess the efficacy/safety profiles and nuances of use of approved and investigational therapies for advanced NSCLC, including cytotoxic, targeted, and immunologic agents
- Describe the role and use of various tumor, patient-, and treatment-related features and factors that should guide treatment selection in NSCLC
- Develop individualized, evidence-based, patient-centric treatment plans throughout the continuum of advanced/metastatic NSCLC

Implement strategies for prevention, timely and accurate detection, and optimal management of adverse effects in patients undergoing treatment for advanced/metastatic NSCLC, to ensure that patients could complete the selected therapy while maintaining maximal quality of life
- Provide adequate disease-, testing-, and treatment-related education and guidance to patients with lung cancer and their family/caregivers, to enable them to meaningfully participate in shared decision-making regarding treatment selection and care planning

Target Audience

This activity has been designed to meet the educational needs of medical oncologists, oncology nurses, pharmacists, and other healthcare professionals involved in the treatment of lung cancer.

Nursing Education Purpose Statement

The purpose of this activity is to improve knowledge and competence of nurses concerning the treatment of lung cancer.

Requirements for Successful Completion

In order to receive credit, participants must view the activity and complete the post-test and evaluation form. A score of 70% or higher is needed to obtain CME/CE/CPE credit. There are no pre-requisites and there is no fee to participate in this activity or to receive CME/CE/CPE credit. Statements of Credit are awarded upon successful completion of the post-test and evaluation form.

Media Enduring Material

Release and Expiration Dates: July 15, 2016 - July 14, 2017
Time to Complete: 120 minutes

Faculty & Disclosure / Conflict of Interest Policy

Before the activity, all faculty and anyone who is in a position to have control over the content of this activity and their spouse/life partner will disclose the existence of any financial interest and/or relationship(s) they might have with any commercial interest producing healthcare goods/services to be discussed during their presentation(s): honoraria, expenses, grants, consulting roles, speakers bureau membership, stock ownership, or other special relationships. Presenters will inform participants of any off-label discussions. All identified conflicts of interest are thoroughly vetted by Medical Learning Institute, Inc. for fair balance, scientific objectivity of studies mentioned in the materials or used as the basis for content, and appropriateness of patient care recommendations.

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Mark A. Socinski, MD, has a financial interest/relationship or affiliation in the form of:
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Mark A. Socinski, MD, does intend to discuss either non–FDA-approved or investigational use for the following products/devices: Various chemotherapies, targeted agents, and immunotherapies alone or in combinations for NSCLC.

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Provider, Credit & Support

Physicians

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Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2.0 MOC points in the American Board of Internal Medicine’s (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider’s responsibility to submit participant completion information to ACME for the purpose of granting ABIM MOC credit.

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Provider, Credit & Support

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This activity is supported by independent educational grants from AbbVie, Celgene Corporation, Genentech, Lilly, and Merck & Co, Inc. For further information concerning Lilly grant funding visit www.lillygrantinfo.com.

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Improving Outcomes With Social Media

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Dr. Socinski: Good evening, and welcome to this educational symposium titled “Non–Small-Cell Lung Cancer Forum: Bringing the Patient to the Forefront of Evidence-Based Lung Cancer Care.” Thank you to those of you joining us. My name is Mark Socinski. Joining me for this PeerView Live event is, first of all, Janet Freeman-Daily, who is a writer, self-proclaimed science geek, lung cancer patient, and activist from Federal Way, Washington. It’s not often that we see patients involved in CME events, so all of us are excited to have her here, to have her share her perspectives and experiences. So thank you, Janet, for being here.

Also among our excellent panel of experts are Dr. Ross Camidge from the University of Colorado Cancer Center, Dr. Anne Tsao from the University of Texas MD Anderson Cancer Center in Houston, and Dr. Naiyer Rizvi from the Columbia University Medical Center.

Narrator: After completing the activity, access the post-test and evaluation form by clicking the red “Get Certificate” button.

Dr. Socinski: So, without further delay, I’d like to introduce our first speaker, our special lead speaker today, Ms. Freeman-Daily. So, Janet, I’ll hand it over to you. Thank you.

Ms. Freeman-Daily: Happy National Cancer Survivors Day. I've taken a path I never would have imagined during my happy days as an undergraduate at MIT. Since receiving a metastatic lung cancer diagnosis 5 years ago and finding effective treatment in a clinical trial, I have repurposed my aerospace systems engineering and writing skills to focus on improving outcomes and quality of life for cancer patients, specifically lung cancer.

I'm going to share with you my experiences using social media to improve patient outcomes. This began shortly after my diagnosis, when I became an e-patient. E-patients are not just patients who go online to find information. They are any patient who is equipped, engaged, empowered, and enabled. I would add that these patients are capable of being equal partners in their care.

Because I became an e-patient, I was able to actively participate as a partner in shared decision-making with my healthcare providers. Online patients and caregivers can find others dealing with the same disease and the same treatment who understand exactly what they are feeling and experiencing. Online communities answered questions I didn’t think to ask my doctors when I was still in shock from my diagnosis. They suggested ways to cope with side effects while I was at home. They prodded me to ask my doctor about symptoms that I hadn’t thought were important. They were available in the wee hours, when the fear was overwhelming. They shared online information resources from reliable sources. I had a support system of thousands available to help me with their experience and hard-won knowledge.
Engaged patients often get better healthcare. Preliminary studies indicate patient engagement and shared decision-making can increase patient satisfaction and outcomes and reduce healthcare costs. Activated patients are less likely to be readmitted within 30 days of discharge, less likely to have poor care coordination, and less likely to lose confidence in their healthcare system.

Most people search for health information online. According to the Pew Research Center, most people use the internet and the majority on a smartphone. 72% of Internet users said they have looked online for health information within the past year (Sep 2012).

The most commonly-researched topics are specific diseases or conditions, treatments or procedures, and doctors or other health professionals.

Half of online health information research is on behalf of someone else—information access by proxy.

60% of Internet users who search online for health information have been helped; 3% say they or someone they know has been harmed.

Sharing information in online patient communities saves lives. The majority of primary lung edema carcinomas have genomic alterations that are treatable either with approved or experimental drugs, yet some metastatic lung cancer patients are still sent home on hospice without genomic testing or knowledge of clinical trials. The online community provides information that helps patients overcome this.

From other e-patients, I learned about molecular testing, genomic sequencing, clinical trials, and how to ask for my data. I also learned I fit the profile of typical ROS1-positive lung cancer patients. The information was something that my local doctors in Seattle knew nothing about.

After my second progression, I arranged to get my tissue tested for ROS1 and enrolled in a clinical trial for crizotinib at the University of Colorado. On this trial, I have had no evidence of disease for three and a half years. I wouldn't have known about ROS1 if I hadn't gone online. Without the online patient community, I would be dead now.
Online communities can be found in disease-centered forums and advocacy organization sites. Each community has a unique structure, features, and moderation style. One forum might attract posts about personal support, and another might talk more about research. Some of these sites aggregate de-identified comments and share them with healthcare providers to help share the patient perspective, while others use donated patient health data for big data analysis.

Some patients form their own disease-specific communities on social media platforms with more familiar interfaces. For instance, cancer patients on Facebook share information and links to journals and news articles, videos from researchers and clinicians, and trusted online resources such as the NCI, ASCO's Cancer.net, and Cancer GRACE.

Twitter offers a variety of communities organized by hashtags, like this one, LCSM, which stands for “lung cancer social media.” The followers of our hashtag, our “tweeps,” include patients, caregivers, clinicians, researchers, advocacy groups, journalists, pharma, and others interested in lung cancer. Our biweekly chats cover topics of interest to all stakeholders.
One recent topic was, how can we overcome hurdles in lung cancer research? Since the hashtag first appeared in June of 2013—not quite 3 years ago—it has been used by over 21,000 different Twitter accounts and generated over 198,000 tweets. It’s even been used to live-tweet a patient’s journey through minimally invasive lung surgery.

Social media can also be used for patient-driven research. I belong to an international online group on Facebook of over 100 patients with different cancers who all have tumors that test positive for ROS1 rearrangements. We contacted researchers and the Addario Lung Cancer Foundation and asked for help in generating more research about our disease.

This collaboration has resulted in a website, shown here, that focuses on ROS1 cancer. And we also generated a patient-driven online survey to gather epidemiological data. The survey asked questions about cancer presentation, lifestyle factors, where we’ve lived, and environmental exposures we might have had. To our knowledge, it’s the first epidemiological study about a genomically driven cancer across cancer types, and it was all made possible by social media.

The Internet and other connected health resources do not replace the counsel of healthcare providers. Research shows patients still consider their providers the most trustworthy source of health information. Online health resources and social media augment health provider services because they answer questions that arise after the patient has left the office. They provide patients with reliable information they can bring to shared decision-making and they encourage patient engagement in their own care.
Don Stranathan, a friend, has a case that’s an excellent example of what social media can accomplish in cancer treatment when combined with shared decision-making. Don’s metastatic lung cancer was stable for 6 years on erlotinib, even though he didn’t have an EGFR mutation. When his cancer started growing again, Don chose to have a large genomic panel run, and this tumor tested positive for an NTRK1 alteration. The test report indicated an ALK/ROS1 inhibitor might be effective for an NTRK1 fusion, so Don and his oncologist decided he should try the FDA-approved drug off label rather than travel to a clinical trial. The day Don picked up the drug, he posted his treatment status and plans on Facebook. By coincidence, that day, I read his Facebook post while I was in Denver waiting to talk to Dr. Bob Doebele, who co-authored the first paper in NTRK1 fusions in lung cancer.

Dr. Doebele said he would really like to talk to Don, and I connected them. Don learned through Dr. Doebele that his NTRK1 alteration was not a typical rearrangement, and other oncologists had found that the ALK/ROS1 inhibitor was not effective for NTRK1-rearranged cancers. This information was not available in any publications. After talking with Dr. Doebele and other oncologists about clinical trial and treatment options, Don decided to start anti–PD-1 immunotherapy with the option of entering a targeted therapy clinical trial if the immunotherapy did not work. He recently had his first scan after 4 months on immunotherapy, and his cancer is responding to it.

Through online resources, access to genomic testing, shared decision-making, and knowledge of clinical trials, we can achieve the best possible outcomes in this evolving era of precision medicine. That’s how social media improves outcomes for patients. I hope you will consider recommending online resources for your patients. Thank you.

Dr. Socinski: Thank you, Janet. We actually just had one question. You had that one slide about the survey of how useful the Internet was. The question relates to that survey, and it was asked, was that survey done through the Internet? And if so, is it possible the answers are somewhat biased? It would exclude people without access to the Internet. Do you want to comment on that?

Ms. Freeman-Daily: That survey was conducted by Pew Internet Research, and they did it with telephone as well as online.
Management of a Patient With Previously Untreated ALK+ Metastatic NSCLC

Dr. Socinski: I'm going to ask Dr. Camidge to come to the podium and, just for the audience, the way that we decided to structure this tonight was both case-based as well as kind of how we manage patients. We first deal with first-line issues and decide on the optimal treatment for the patient, institute the treatment, and then obviously at some point the treatment fails the patient and you get into the issues of second-line.

So we're going to divide up our discussion of these sorts of things into first-line issues and then, in the second hour, second-line issues. So, having said that, I'll turn it over to Ross for discussion of managing previously untreated ALK-positive metastatic non-small-cell lung cancer.

Dr. Camidge: Good evening. So we're going to talk about the patient who walks through the door and turns out to be ALK-positive. So here's our case. So, a 23-year-old male, never-smoker. He had a rapid-onset chest pain and dyspnea, no other symptoms. He was admitted to the ICU. Cardiac tamponade was diagnosed. The pericardial fluid was drained. The pericardial biopsy showed CK7-positive, TTF1-positive adenocarcinoma cells. Additional testing showed that he also had lesions within his lung, mediastinal lymph nodes, and liver. An MRI of his brain showed a single 14-mm asymptomatic left frontal lesion, as well. He was stabilized, he was discharged, he comes to your clinic, and the testing on that pericardial biopsy was done by FISH, and it shows that 25% of his cells show a split signal.

They drained the fluid. Actually, they put a pericardial window in. And from the fluid in the pericardial biopsy, he appeared to have CK7-positive, TTF1-positive adenocarcinoma. Additional testing showed that he also had lesions within his lung, mediastinal lymph nodes, and liver. An MRI of his brain showed a single 14-mm asymptomatic left frontal lesion, as well. He was stabilized, he was discharged, he comes to your clinic, and the testing on that pericardial biopsy was done by FISH, and it shows that 25% of his cells show a split signal.

So what are ALK-positive patients like? Well, most of them are never-smokers, but not all of them. Smoking is common, often with a relatively low history, but the majority of patients have no smoking history, like this case we described. The most of the cases are adenocarcinoma, and some of them also have card-carrying squamous cell patients who have an ALK rearrangement.

There is a tendency for this to be present in younger patients. Those seem to be about a decade, decade and a half younger than most lung cancer patients. But there's a huge range. My youngest patient was 14 when she was diagnosed, my eldest 82. The initial data that came out suggested there was a male preponderance, but that hasn't panned out in later series, and it now looks like there's an equal sex ratio between males and females.
So one of the interesting things as we started to see a lot of these patients is they seemed to have a particularly interesting pattern of metastatic spread when they were first diagnosed. And why shouldn’t they? These are different diseases. These different oncogenes have different signaling inside the cell, different behavior. And it turned out that at diagnosis with metastatic disease, ALK has a particularly high incidence of pericardial disease, higher than EGFR, KRAS, or triple wild-type in this particular study. It also has a higher incidence of pleural disease, and you can see on the far right that both ALK and EGFR have a higher incidence of liver disease compared to KRAS and others.

This is not a substitute for testing, but this is what we as physicians like to do in the clinic, a little bit of Victorian showmanship. We think this patient is more likely to have ALK because they have pericardial disease and they’re a never-smoker, and sometimes we’re right. But we should still test.

How do we test? Well, there are now a series of FDA-approved tests. Initially, it was the FISH assay, which I’ll show you in a little bit more detail, but now immunohistochemistry is approved, and many people are doing PCR or, increasingly, next-generation sequencing to find these gene rearrangements. The latest NCCN iteration suggests that molecular testing should be done as part of a molecular panel that includes EGFR and ALK, and the idea is that you will also pick up some other actionable abnormalities.

Now, one of the questions was, is 25% borderline? Well, it turns out that the way the FISH works is you’re looking for a split signal. So this is a rearranged gene. There are red and green probes on either side of the normal form of the gene. And when the rearrangement occurs, another gene—the donor gene—sits in the middle of those two probes, and so they separate and that’s the split signal.

So one of the interesting things as we started to see a lot of these patients is they seemed to have a particularly interesting pattern of metastatic spread when they were first diagnosed. And why shouldn’t they? These are different diseases. These different oncogenes have different signaling inside the cell, different behavior. And it turned out that at diagnosis with metastatic disease, ALK has a particularly high incidence of pericardial disease, higher than EGFR, KRAS, or triple wild-type in this particular study. It also has a higher incidence of pleural disease, and you can see on the far right that both ALK and EGFR have a higher incidence of liver disease compared to KRAS and others.

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Now, because you have observer error, because DNA can get stretched when you prepare these things, because the microtome sections cells and can go through between these things, you can see a certain background noise. So if you look in the right-hand three columns, you can find split signals in up to about 11% of cells, either in normal tissue, or even in the tumors of ALK-negative cases.

If you look in the far left-hand column, the other interesting thing is in those which are ALK-positive, it’s not 100% of cells showing a split signal, and it’s not because it’s a subclone, it’s really because you’re missing it in some cells. They’re false cellular negatives. You microtome a section between it, they’re out of the plane of section, the probes didn’t hybridize properly, or just observer error. And the original 15% cutpoint—which is in the FDA label—appeared to separate most of the signal from most of the noise.
I draw your attention to one of the posters at this year’s ASCO led by Jean-Charles Soria looking at over 1,000 cases in some of the Pfizer studies looked at retrospectively. And they tried to see how many in the ALK-positive cases really came up and sort of kissed that 15% cutpoint, and therefore really would have been borderline positives. And it was a relatively small number. We previously published it was running about 15% or 16%. This was much closer to 2% or 3%. So most of the time you won’t have a borderline call. If you did, if you actually get a readout that says this is 16% positive or 14% positive, you might want to go back and say, “Could you do a separate diagnostic test, either immunohistochemistry or a sequencing assay?”

One of the other questions was looking at if platinum-pemetrexed is ineffective, was how the wording was. This is the PROFILE 1014 phase 3 study, first-line study, crizotinib vs platinum-pemetrexed in an ALK-positive population. You can see that clearly the response rate and the progression-free survival are better with the crizotinib than with the chemotherapy. But the chemotherapy is not ineffective. It has a response rate of over 40%, and interestingly enough, in this study, you were mandated a fixed number of cycles of the doublet, but with no mandated pemetrexed maintenance therapy, and you can see that the curve for the chemotherapy falls away when you stop giving the pemetrexed.

Now, we are getting a large number of next-generation ALK inhibitors. Ceritinib now has a license. Alectinib now has a license. And brigatinib has got breakthrough status from the FDA and probably may have a license by the end of the year or the beginning of next year. And in the post-crizotinib setting, these more potent drugs which have an activity against a range of resistance mutations are producing response rates in the 50%-70% range, with median progression-free survivals running between 7 and over a year in the case of brigatinib. But note that these are not first-line licenses. So that’s why the question said immediate FDA licensed therapies do not include alectinib and ceritinib currently.

I draw your attention to brigatinib, the new kid on the block, because there are some updates at this year’s ASCO. We’re seeing some more data in a larger phase 2 study which is showing about a 55% response rate, but still a median progression-free survival over a year.
What about within the brain? Remember, this patient had a solitary brain metastasis. And one of the questions was, crizotinib is ineffective in the brain. Well, that kind of story emerged because a lot of patients on crizotinib were failing in the brain. So in our initial series, 46% of those who first progressed were progressing in the brain, and in 85% of those cases, that was the only site of progression at the time.

Later, Dan Costa from Beth Israel led a single case report looking at matched blood and CSF samples and showed a very small proportion, less than 0.3%, of the levels in the blood getting through into the brain.

And finally, Dan also led a large study retrospectively of the crizotinib data set and I think here we show not that the activity of crizotinib in the brain is zero, but for every metric—be it response rate, duration of response, or progression-free survival—it’s lower in the brain than elsewhere. So it’s not zero, but it’s less.

And so this is at least my own personal flow diagram. And a colleague of mine, Martin Edelman from Maryland, had said, “You’re never going to get consensus on how to manage brain mets.” And it’s not because I want to try and show that there is a consensus, but I want to introduce the idea of reasonable doubt. So if you had an ALK-positive patient who had disease in the brain, what you might first want to ask is, is it symptomatic or asymptomatic? If it’s asymptomatic, because the activity of crizotinib in the brain is not zero, and currently it is the only licensed first-line ALK inhibitor in the USA, you might start them on crizotinib and see if they’re in that 18% that responds. And then we can talk about what you do if it progresses later. Now, there are some first-line trials you could also put them on.

If they’re symptomatic, many of my colleagues—including Anne, here, because we were on an advisory board the other day—would say that, to me, symptomatic is enough that you need to go for radiotherapy. And in the setting of radiotherapy, the cutpoint is really depending on the number of lesions. If it’s below a certain number, you can probably get away with stereotactic radiosurgery. Above a certain number, you want to give whole-brain radiotherapy. Again, this is all in the absence of some of those second-generation drugs.

I’m going to show you a flow sheet for what happens if you progress whilst you’ve actually started the crizotinib in one of the later presentations.

These are some of the things pushing some of those drugs into a first-line setting. So this is ceritinib. This study has completed accrual, and we’ll probably see this data maybe at the end of this year or at ASCO next year. Note that this one was compared to chemotherapy, like the PROFILE 1014 study, but this included pemetrexed maintenance. So it’s going to be an interesting study to see the result of, because although we have potentially a more potent drug—ceritinib compared to a first-generation drug, crizotinib—the control arm is also going to do a lot better.
These other studies are also about to read out. This is alectinib, one of the next-generation drugs, compared to crizotinib in the first-line setting. This is the J-ALEX study. Note that it’s slightly different from the ALEX study, which is conducted in the rest of the world. The J-ALEX study was only conducted in Japan. You’re allowed to be chemotherapy naïve or have one line of chemotherapy first. It has a different dose than the study used in the rest of the world. The Japanese had capped the dosing at 300 mg twice a day for some formulation issues, but ALEX has got a higher dose.

But what we do know is that this study of alectinib vs crizotinib is resoundingly positive in favor of alectinib. The median progression-free survival of crizotinib is about 10 months, as you might expect. The median for the alectinib arm has not yet been reached, but the lower limit of the confidence intervals is 21 months and counting. So it’s really quite amazing. The hazard ratio is 0.34.

And so when we started to do these studies, we always had this question. You have a drug that you could use sequentially, a second-generation drug after crizotinib. And so if you were going to use the second-generation drug first, was it just going to beat it? Was it going to be a positive study, but no one would care, because you could use the drug sequentially? Was it going to be the same as sequential therapy, in which case people would only care if it was cheaper or less toxic? Or was it really going to change the natural history of the disease?

And the J-ALEX data suggests that that may be going on. And why is it changing the natural history of the disease? Because when you allow that first clone to flare up so that you have clinically apparent acquired resistance, the area under the curve is dividing cells, and they’re generating the diversity that leads to the next and the next mechanisms of acquired resistance. And if you suppress them all from the get-go, then maybe you change the natural history of the disease and extended that control.

Dr. Socinski: Thank you. I’m going to ask Anne to come to the podium. But while she’s getting up, Janet, there was one other question. This Internet thing, I think, has created some interest. Have you found that Internet groups add to anxiety—for instance, when patients don’t do well?

Ms. Freeman-Daily: Some of the groups are better moderated than others. So some of them, I will admit, when you log on all you see is the headlines of the various threads. And in some cases there are a lot of people who are not doing well, and you see that, and that can be disheartening. But there are other groups that are very well moderated, and you can go and find the information you want, and you don’t have to necessarily go through all of the threads where people are having difficulty.
Management of a Patient With Previously Untreated EGFR+ Metastatic NSCLC

Anne S. Tsao, MD
The University of Texas MD Anderson Cancer Center
Houston, Texas

Case 2

- 65-year-old minimal former-smoker Hispanic female patient presents with cough, SOB, and mild left shoulder pain. A PET-CT scan shows multiple bilateral pulmonary nodules, left adrenal metastases, and numerous bone metastases including a left scapular metastasis.
- A biopsy of a lung nodule shows adenocarcinoma that is cytokeratin and TTF1 positive.
- The tumor tissue is sent for genetic profiling and returns back positive for EGFR mutation del exon 19.
- Guardant 360 testing confirms the EGFR mutation del exon 19.

Dr. Tsao: Thank you for being here tonight. So this was a patient of mine, a 65-year-old minimal former smoker, a Hispanic female, and she came in with cough, shortness of breath, and mild left shoulder pain. Did a PET-CT scan on her, and she was found to have multiple bilateral pulmonary nodules, left adrenal metastases, and numerous bone metastases, including a left scapular metastasis, which is where her pain was at. She had a biopsy of the left lung nodule, which showed adenocarcinoma. It was TTF1-positive. I sent it for genetic profiling, and it came back as EGFR mutation deletion exon 19. I also sent it off for Guardant 360 testing, which also confirmed the mutation at deletion exon 19.

Obviously, EGFR mutations are found in 10%-15% of all of our lung cancer patients. They are predominantly through exon 19 through 21, but EGFR mutations are not the same. There are many ones that we have determined to be actually clinically relevant, but you really do have to know three of them. The deletion exon 19 and the L858 are the ones that are sensitive to our first- and second-generation EGFR TKIs. The T790 mutation is a resistant mutation.

So these are just very quick pictures. This is a patient with a deletion exon 19. You can see from the December 2000 CT scan, this is a patient who we would have put into hospice normally, but after 2 years still had complete clearance on the EGFR TKI.
But the T790 mutation is relevant because it's an amino acid change that alters the protein structure. And it alters the binding pocket of the receptor so you can no longer bind the first-generation EGFR TKIs, the erlotinib and the gefitinib. But as we'll get to in another section of the lecture, there is now drugs that target the T790, specifically osimertinib.

Now, obviously, over time we do get resistance, and so you've seen these pie charts ad nauseam.

Now, all of you know the IPASS trial. We're really going back in the data. This was a phase 3 trial that was a landmark study that first showed that an EGFR TKI was better than chemotherapy for EGFR-mutant patients. Now, that trial actually didn't do genetic profiling because it was done so long ago. It just had pretty much never-smokers with adenocarcinoma or minimal former smokers.

And essentially, when you looked by EGFR mutation status, you can see that those who got gefitinib and had an EGFR mutation had the best progression-free survival, and those who did not have the mutation that got gefitinib had the worst. So very important to know the mutation status of your patient before you treat. Now, EGFR mutation is a prognostic variable, where these patients generally tend to do better. For the most part, they tend to be minimal former smokers or never-smokers, although you can still pick this up in smoking patients. So we recommend screening all adenos for this. But for the most part, in general, they do better overall.

And the bottom line was that the erlotinib was favored with progression-free survival, with a response rate about 58%.

Now, the EURTAC trial was a study that was also phase 3 looking at erlotinib compared to chemotherapy.

New, the EURTAC trial was a study that was also phase 3 looking at erlotinib compared to chemotherapy.
Now, the third EGFR TKI that’s approved for front-line use is afatinib. This is different from the other two EGFR TKIs in that it’s an irreversible EGFR tyrosine kinase inhibitor. It also tends to be what we call a pan-HER family blocker.

And so this was the LUX-Lung 3 study. I’m not going to show you LUX-Lung 6, but essentially it’s close to being identical to this, except it was conducted in Asia. In the LUX-Lung 3 study, patients were screened, and if they had an EGFR mutation they were enrolled onto the trial and randomized 2 to 1 to the afatinib at 40 mg/day vs chemotherapy. And their primary endpoint was progression-free survival.

Now, across the board for response rate, the afatinib arm was favored.

And then also, when we look at progression-free survival, the afatinib actually had an improved progression-free survival.
Now, when we look at progression-free survival, the afatinib had a better PFS. The hazard ratio was 0.73. The P value statistically significant at 0.017.

When we look across the subgroup analysis, pretty much across the board, most all the subgroups seemed to favor the afatinib arm.

Now, the LUX-Lung 7 trial was actually a head-to-head comparison of afatinib vs gefitinib, and this included patients who had an L858 or deletion exon 19 mutation. And there are 319 patients that were randomized. They were stratified by presence of brain metastases or EGFR mutation status, and their primary endpoint was progression-free survival. Now, the gefitinib dose used here was 250 mg/day, and the afatinib was 40 mg/day.
So in terms of toxicity, there was one fatal case in the gefitinib arm: there was a renal and hepatic failure. In the afatinib, though, overall had more adverse events than the gefitinib. There was more ≥ grade 3 diarrhea, rash, and fatigue. But gefitinib apparently in this trial had a little bit more increased LFTs and rash or acne was only 3%. So when we looked at the serious adverse events, afatinib was 11% vs 4% in the gefitinib arm, so the sense was that maybe afatinib is more difficult to take than the gefitinib. Of note, though, the gefitinib had a 3% interstitial lung disease rate vs none in the afatinib arm.

And when we looked at response rate, objective response rate favored the afatinib at 70% vs gefitinib at 56%, and that was statistically significant.

When we look specifically by mutation—these are the waterfall plots—you can see that pretty much both drugs do give you responses. The afatinib, however, may have a little bit more.

So, to summarize, in the front-line space what you do for TKIs, you want to always be sure you know your mutation before you treat them. There are some rarer mutations that you actually have to go online—and I Google it—to see whether or not there’s a collective database about which ones might be sensitive versus which ones that aren’t.

You do have your choice between gefitinib, erlotinib, and afatinib in the front-line indication. And it really just depends,
NSCLC Forum: Bringing the Patient to the Foreground of Evidence-Based Lung Cancer Care

I think, on your patient. If you have a really elderly patient who probably can’t tolerate a lot of rash and diarrhea, then gefitinib may be an appropriate choice for them; whereas you may have a deletion exon 19 young patient in their 30s who wants to be maximally aggressive, and they may be a good candidate for the afatinib. And so you really do have to tailor your choice of the EGFR TKI based off of what your patient looks like and how well they’re doing.

Treatment-Naive EGFR\text{MUT} Patients EGFR TKIs vs Chemotherapy\textsuperscript{1-8}

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>Median PFS, months</th>
<th>Median OS, months</th>
</tr>
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<tbody>
<tr>
<td>Maemondo</td>
<td>Gefitinib vs Carboplatin/Paclitaxel</td>
<td>230</td>
<td>10.8 vs 6.4 (P = .001)</td>
<td>30.5 vs 23.6 (P = .31)</td>
</tr>
<tr>
<td>Mitsudomi</td>
<td>Gefitinib vs Carboplatin/Cisplatin</td>
<td>177</td>
<td>9.2 vs 6.3 (P = .0001)</td>
<td>36 vs 39 (HR = 1.15)</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>Erlotinib vs Carboplatin/Cisplatin</td>
<td>165</td>
<td>13.1 vs 4.5 (P = .0001)</td>
<td>18.3 vs 19.8 (P = .37)</td>
</tr>
<tr>
<td>EURTAC</td>
<td>Erlotinib vs protein-based Chemotherapy</td>
<td>174</td>
<td>9.7 vs 5.2 (P = .0001)</td>
<td>18.3 vs 19.8 (P = .37)</td>
</tr>
<tr>
<td>LUX-Lung 3</td>
<td>Afatinib vs Carboplatin/Gemcitabine</td>
<td>307</td>
<td>13.0 vs 6.9 (P = .0001)</td>
<td>31.6 vs 28.2 (P = .1990)</td>
</tr>
<tr>
<td>LUX-Lung 8</td>
<td>Afatinib vs Carboplatin/Gemcitabine</td>
<td>324</td>
<td>11.0 vs 5.6 (P = .0001)</td>
<td>23.6 vs 23.5 (P = .1756)</td>
</tr>
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*Common mutations only.


There was one more thing I wanted to mention about this, and that’s a new combination. And this was presented at last year’s ASCO by the Japanese group, and this bevacizumab plus the erlotinib combination.

Now, I just want to mention what happens when you’re waiting for genetic profiling and this patient gets chemo. The EGFR mutants respond to the chemo, and so if they get one or two cycles of chemo, you get the profiling back, you have your choice about whether to do four total cycles and switch, or you could switch after two cycles. And we still don’t know whether or not that has any impact on their case. But I generally try to advise people to go ahead and switch as soon as possible once you know their mutation status.

Bevacizumab + Erlotinib Combination

The combination of bevacizumab + erlotinib may cause simultaneous blockade of VEGF and EGFR signaling pathways resulting in synergistic antitumor effects.\textsuperscript{1}


And in this study, it was actually a smaller study, but they were looking at EGFR mutants, and bevacizumab-erlotinib vs erlotinib alone.

Primary Endpoint: PFS by Independent Review\textsuperscript{1}

<table>
<thead>
<tr>
<th>N</th>
<th>Median, months</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
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<tbody>
<tr>
<td>100</td>
<td>10.3</td>
<td>1.64</td>
<td>0.96-2.86</td>
<td>.07</td>
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*logrank test, trended |

1. Katz T ASCO 2014

And in this, the bevacizumab-erlotinib arm actually had a superior progression-free survival.
Dr. Rizvi: Yeah, so I think that there’s some controversy around that in terms of a differential benefit between afatinib and erlotinib in exon 19 deletion vs L858R mutations. And I think that these sorts of subset analyses I’m not really sure how to interpret, so in general, my practice is to favor erlotinib as my sort of TKI of choice irrespective of mutation status.

Dr. Socinski: Yeah. I think there’s that meta-analysis that shows that the exon 19s are just more sensitive, at least if you measure by PFS hazard ratio, than the exon 21s. The fact of the matter is that the afatinib folks have all the data in exon 19. It doesn’t mean it doesn’t have the same class effect with the other agents is how I read it there.

Dr. Rizvi: I have a question for the group around bevacizumab.

Dr. Socinski: Yeah, I was going to ask that question.

Dr. Rizvi: Because I think it was approved in Europe.

Dr. Socinski: In combination?

Dr. Rizvi: With erlotinib, wasn’t it?

Dr. Socinski: Yeah.

Dr. Rizvi: So, I mean, I have not been routinely adding bevacizumab to erlotinib in my practice. I’m not sure if there is insurance issues around that as well. But I don’t know what other people like Anne or Ross?

Dr. Tsao: We’re not doing it off study.

Dr. Camidge: So I haven’t. It’s interesting, the EMEA chose to take a pure Japanese study and issue a license on the basis of that, presumably with the promise that some Western data would be coming. It certainly is intriguing data. We understand the biology. But I would wait for something definitive. And also, it’s hard for a patient to say, “You can have a tablet, or you can reattach the leash to the infusion center.”

Dr. Socinski: Yes. It medicalizes the treatment, right?

Dr. Camidge: Yeah.

Dr. Socinski: I mean, they’re coming in every 3 weeks. And I don’t do it in my practice. I think we’d need more evidence, and we only have PFS. We don’t know the impact of overall survival. There was a question about gefitinib being commercially available. Yes, it was approved, again, the second time, what, 6, 8 months ago?

Dr. Rizvi: Yeah, sometime in 2015. Yeah.
Initial Management of a Patient With Metastatic Non-Squamous NSCLC With No Driver Mutation

Dr. Socinski: Well, we're going to switch gears. So we've talked about the two actionable oncogenic drivers, if you will, and this is a very nice example where molecular testing and finding these things in the clinical trials that we reviewed has really changed the standard of care for those molecular subsets to a TKI-based approach rather than cytotoxic chemotherapy. We're going to switch gears a little bit, and we've asked Ross to kind of walk us through initial management of a nonsquamous metastatic non–small-cell with no driver mutation. So, Ross?

Dr. Camidge: So, hello, again. Here I am, the hardest-working man in show business, second talk. So one of the questions I want you to consider is, what do we mean by no driver? We're going to start with a case, again, and questions. A 65-year-old female with 15 pack year history, quit 20 years ago. Yes, I'm not going to give you a nice, clean case. It's going to be somewhere in the middle. Presents with cough and weight loss, and you can see from the PET scan, widespread disease in the lungs, mediastinal lymph nodes, abdominal lymph nodes, and liver at diagnosis. In this case, the central nervous system was clear. They did a liver biopsy, TTF1-positive adenocarcinoma—again, it's a lung cancer. It was ALK FISH-negative and EGFR-negative by a next-generation sequencing assay.

All right, so let's start from the beginning. So as we've already heard, there are a couple of groups which have already pulled themselves out from the standard first-line chemotherapy treatment of nonsquamous lung cancer: EGFR; we've heard there are licensed first- and second-generation EGFR TKIs; erlotinib, gefitinib, and afatinib; and ALK has crizotinib licensed in that setting. As you've heard, there's a little bit of a battle going on. Osimertinib, one of the third-generation drugs which is licensed, is exploring activity in the first-line setting. That's called the FLAURA study. That might read out next year. And we've already heard the J-ALEX data, and the ALEX data will read out maybe this time next year. And so second-generation ALK TKIs are trying to nudge in there.

So what do we do for the remainder, that nonsquamous box that doesn't have either an ALK or an EGFR? So I'm going to ask you to think about the non-driver population in two ways. So as we've already heard, there are a couple of groups which have already pulled themselves out from the standard first-line chemotherapy treatment of nonsquamous lung cancer: EGFR; we've heard there are licensed first- and second-generation EGFR TKIs; erlotinib, gefitinib, and afatinib; and ALK has crizotinib licensed in that setting. As you've heard, there's a little bit of a battle going on. Osimertinib, one of the third-generation drugs which is licensed, is exploring activity in the first-line setting. That's called the FLAURA study. That might read out next year. And we've already heard the J-ALEX data, and the ALEX data will read out maybe this time next year. And so second-generation ALK TKIs are trying to nudge in there.

So what do we do for the remainder, that nonsquamous box that doesn't have either an ALK or an EGFR? So I'm going to ask you to think about the non-driver population in two ways. So the first is, well, there are actionable abnormalities. You remember, I said the NCCN panel says, “Do broad molecular testing because you can pick up other rubies in the dust.” And those I'm going to give you examples of—ROS1 rearrangements, BRAF V600E mutations, and MET exon 14 skip mutations.
So let's start with those. ROS1 fusions. How could anyone have said there is no actionable mutations when Janet is here? She has a ROS1 gene rearrangement. Come on, guys. All right. And it got actually an extension of the original crizotinib label in March of this year. So, interesting. So we already have the safety data, and now you have a defined molecular subgroup with probably only about 50 patients in it. But the waterfall plots look very similar to ALK-positive disease, and in fact, if anything, the median PFS is better.

BRAF V600E— that same mutation you get in melanoma, that same mutation you get in colorectal cancer—there was a big debate, given that they respond beautifully in melanoma and don't respond in colorectal cancer to BRAF inhibition. What was lung cancer going to be like? Well, fortunately, lung cancer turned out to be more like melanoma. This is data on the combination—just like in melanoma—of a BRAF and MEK inhibitor, dabrafenib and trametinib, and that combination received FDA breakthrough status in 2015, and this will probably become a licensed treatment sometime either by the end of this year or early next year. And it has a 63% response rate. It’s about 2% of adenocarcinoma of the lung. But if that 2% was your mother, you'd want to know.

What about MET? Well, MET has been a little bit of a work in progress. The first one, which most people agree on, is these things called MET exon 14 skip mutations. They trim off the ubiquitination domain of MET, and therefore the protein is stabilized. It hangs around longer. They are hard to find because the mutations occur in multiple different places, even though they end up with the same result. Therefore, RNA-based assays are actually preferential. Many of the NGS sequencing panels will miss these, but that's a work in progress, and you'll see as people have realized the importance of these, some of the foundation medicines are expanding to capture these.
Activity of ALK Inhibitor Therapy in Advanced MET Exon 14-Altered NSCLC

- MET exon 14 alterations are actionable lung cancer drivers that can be detected in the clinic and should be screened for.
  - Occur with a frequency comparable to ALK-rearranged lung cancers
  - Crizotinib has clinically meaningful antitumor activity in patients whose lung cancers harbor a MET exon 14 alteration

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<tr>
<th>Response-Evaluable Population (n = 18)</th>
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<tr>
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<tr>
<td>Best overall response, n (%)</td>
</tr>
<tr>
<td>Unconfirmed CR/PR†</td>
</tr>
<tr>
<td>ORR (95% CI; 22/59; n = 6/10)</td>
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* Of the 5 patients, 2 achieving confirmation, 3 cannot be confirmed.
† This patient discontinued therapy in cycle 4; response imaging could not be performed but response evaluable per protocol.

It turns out that cutpoint has to be very high. Many of the early studies which produced confusing signals were trying to include too many people. It turns out that very high level of MET amplification, which is a ratio of MET to the centromere on chromosome 7 of 5 or greater, is probably only about 1% of adenocarcinoma, and they respond very well to MET inhibitors, too. There is some overlap with MET exon 14 skip mutations, but not completely. And we believe that either can be a true driver state. And I’ve mentioned Alex’s study, which is going to be presented tomorrow.

You will see data when Alex Drilon will show that in about 4% of adenocarcinoma of the lung, there are these MET exon 14 skip mutations, and they respond beautifully to a MET inhibitor. In fact, we’re using our old friend crizotinib as a MET inhibitor here. But it could equally be anyone else’s MET inhibitor, and they’re running about a 45% response rate. So it’s a true driver state.

You can pull those ones off, and when you start to say to your patient, “I’m sorry, you don’t have an actionable mutation”—particularly if your patient is Internet-savvy and knows people like Janet—they’re going to say, “What haven’t you tested me for?” But when you’ve actually gone through what are current lists, which would include ROS, BRAF, and MET, then you can say, “Maybe we don’t have an actionable abnormality.” And in that situation, that’s where you’re going to talk about immunotherapy.

The area of controversy is MET amplification. So just increases in the copy number of the gene has also been explored. And this is data I presented at ASCO a couple years ago. Here, this is a continuous variable. It’s not categorical. It’s not “you have the mutation or not.” It’s a continuous variable, copy number of the gene. Where do you put the cutpoint to say this is highly amplified in a way that matters, that makes it predictive of response to a MET inhibitor, vs this is negative?

<table>
<thead>
<tr>
<th>MET Exon 14 variants</th>
<th>Low MET n = 2</th>
<th>Intermediate MET n = 6</th>
<th>High MET n = 6</th>
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<tbody>
<tr>
<td>MET amplification (MET:CEP7 ≥ 5)</td>
<td>0.3%–1% adoço</td>
<td>4% adoço</td>
<td>14% adoço</td>
</tr>
<tr>
<td>ORR (confirmed)</td>
<td>16 (17%)</td>
<td>8 (13%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>ORR (confirmed): DoR: 16 weeks</td>
<td>9 (9%)</td>
<td>0 (0%)</td>
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SO is defined as needing SD for 5 weeks.


So you can pull those ones off, and when you start to say to your patient, "I’m sorry, you don’t have an actionable mutation”—particularly if your patient is Internet-savvy and knows people like Janet—they’re going to say, "What haven’t you tested me for?" But when you’ve actually gone through what are current lists, which would include ROS, BRAF, and MET, then you can say, "Maybe we don’t have an actionable abnormality." And in that situation, that’s where you’re going to talk about immunotherapy.

PD1 Monotherapy in 1st Line? Historical Control Data

<table>
<thead>
<tr>
<th>Summary of OS, PFS, and Response Rate by Histologic Group for 3 Pretreated Trials</th>
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<tbody>
<tr>
<td>Histologic Group</td>
</tr>
<tr>
<td>Squamous carcinoma (n)</td>
</tr>
<tr>
<td>Path (n)</td>
</tr>
<tr>
<td>Median OS (mo)</td>
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<tr>
<td>HR (95% CI):</td>
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<tr>
<td>Median PFS (mo)</td>
</tr>
<tr>
<td>HR (95% CI):</td>
</tr>
<tr>
<td>Response rate (%)</td>
</tr>
<tr>
<td>Non-squamous (n)</td>
</tr>
<tr>
<td>Path (n)</td>
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<tr>
<td>Median OS (mo)</td>
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<tr>
<td>HR (95% CI):</td>
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<tr>
<td>Median PFS (mo)</td>
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<tr>
<td>HR (95% CI):</td>
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*(n=number of patients: *n* is the number of patients in each category.

Now, when we're talking about immunotherapy in the first line—not in the second line. So in the second line, Naiyer's going to go on and talk about that, where we know there's about a 20% response rate and there's a median progression-free survival of 2 or 3 months. In the first line, you have to think, what are you trying to compete against? And you can see from this historical data, when we're talking nonsquamous lung cancer with first-line doublet chemotherapy, we're talking about a median progression-free survival of about 5 months, an objective response rate of 20%-30%. So that means that's the hurdle any randomized study of PD-1 monotherapy has to get over. And an unselected population—so this was an unselected patient—will not clear that hurdle. And therefore, every single company which is exploring PD or PD-L1 monotherapy in the first-line setting says, "We will not go in an unselected population." Instead, they enrich for benefit. And how do you enrich for benefit? Well, you have to do some kind of assay to kind of rule out those who are less likely to benefit and rule in those who are more likely to benefit. There's not an absolute test. This is not an on or off switch like an EGFR mutation. This is much more like a dimmer switch. You get to dial up how much on you want.

So here we'll illustrate it. So unselected isn't going to get over the hurdle of first-line chemotherapy, so somehow we have to get rid of the sad Naiyer, who can't get over it. He's not getting much benefit from PD-1, and we have to get the big Naiyer who can leap over the hurdles. So how do we enrich for the big Naiyer? Well, the big Naiyer, you have to understand, is actually composed of two groups of people: the really big Naiyer, who is getting unequivocal benefit, and a whole group of people who might be getting a little bit of benefit.

So there are two approaches which drug companies are taking. They're using PD-L1—which, bear in mind, you can dial up or down. If you choose a PD-L1 enrichment—so you're trimming down your people maybe to about 25% of the lung cancer population, so that's a pembrolizumab approach—you're going to get a rarer population, but it's going to really clear that hurdle. Okay? That's the rare, big Naiyer. And with that approach, with the patient sitting in front of you, you're not going to say, "Well, you're kind of in equipoise with chemotherapy, but maybe it's a little bit better than chemotherapy." You're going to say, "I really think this treatment's likely to work for you." The alternative approach is—remember, a license is based on beating a comparator—is to have the minimal necessary enrichment to just beat your comparator.

So essentially what you're doing is, you're taking the big Naiyer, and you're diluting him with lots of little Naiyers to essentially say, "What is tolerable dilution of benefit in order for me to get a positive study?" And that would be any company that wants to lower the hurdle of PD-L1 enrichment to just make it high enough to clear that hurdle. And Naiyer should hopefully be able to comment on some of this in terms of those two approaches. They're not medical approaches, they're business approaches.
And I show you this as an example just of the chemotherapy. So this is the study with atezolizumab. This is three different platinum doublets adding in atezolizumab. This is just a small phase 1 study. But you can see, they’re getting response rates which are running sort of 60%-70%. What we haven’t seen is, are these immunotherapy-type responses—ie, they’re long-lived? Our only data is if you look at the spider plot there, you can see some of them are long-lived and some of them aren’t. But we will get the outcome when it comes out in phase 3 studies.

The reason I show you this, and the reason I flag up this abstract is this is an interesting abstract also from the FDA: they’re using their large data set, and they’re showing some interesting data that the depth of response—not just if you get a partial response or not, but the depth of response—actually correlates with overall survival. And that brings to the idea that maybe suddenly not just the response rate, but for example the complete response rate might start to become important with some of these studies. And certainly, if you look on the right-hand side they have a higher complete response rate.

**Dr. Socinski:** Ross, one quick question here. And the question is, “How about MET overexpression? Isn’t it true that amplification would lead to overexpression? How much expression will the cutoff of 5 translate into?” So could you clarify that?

**Dr. Camidge:** So, you’re absolutely right. So immunohistochemistry has been used. Again, that’s a continuous variable. You have to look at how good we are at quantifying immunohistochemistry. There’s an interesting study led by the Chinese at this meeting here looking at MET as an acquired resistance driver in the EGFR mutant population. And they could show that when they enriched for a kind of 3+ IHC, certainly the combination of an EGFR TKI and a MET TKI had a reasonable response rate in the acquired resistance setting, but it was much more impressive when your method of enrichment was based on gene copy number, and not just IHC. So I think yes, it gets you closer to it, but it’s still such a messy technique that gene copy number is a little better.
Initial Management of a Patient With Metastatic Squamous NSCLC

Anne S. Tsao, MD
The University of Texas MD Anderson Cancer Center
Houston, Texas

Case 4

- 68-year-old Caucasian male patient with 90 pack year smoking history presents with 10-pound weight loss, cough, and SOB. CT scan showed a 5-cm RUL lung mass, bilateral mediastinal and supraclavicular lymph nodes, 2 additional lung nodules in the RLL and LUL, and 2 liver metastases

- A biopsy of a supraclavicular lymph node shows squamous cell carcinoma that is cytokinin and TTF1 positive

- The patient is interested in immunotherapy but not clinical trials

Dr. Tsao: All right, so this is case number 4. This is a 68-year-old patient, a Caucasian male. He has a 90 pack year smoking history and a 10-pound weight loss with cough. A chest CT shows a 5-cm right upper lobe lung mass, bilateral mediastinal supraclavicular lymph nodes, and two additional lung nodules in the right lower lobe and left upper lobe. And then he's got two liver mets. A biopsy of the supraclavicular lymph nodes shows squamous cell carcinoma, and it's TTF1-positive. The patient wants immunotherapy, but does not want to go onto a trial. So what would you recommend?

So this is right now my algorithm for someone who has no actionable mutation. And when we specifically look at the squamous cell carcinoma population, you definitely want to avoid pemetrexed, and you want to avoid bevacizumab in the front-line setting. We don’t give pemetrexed because pemetrexed targets the folate pathway, so there’s something called thymidylate synthase. And squamous cell carcinoma has high levels of thymidylate synthase, so it’s an intrinsic mechanism of drug resistance, so pemetrexed doesn't work for squames.

Tsao Algorithm: No Actionable Mutations 2016

Tsao – SCC algorithm 2016
Also, bevacizumab can predispose these squamous cell carcinoma patients to fatal pulmonary hemoptysis. So there is no indication for bevacizumab in the front-line setting for squamous cell. So what options do we have? Well, you could do a platinum doublet with a taxane, nab-paclitaxel, gemcitabine, vinorelbine. But what recently got FDA approved was a platinum doublet with necitumumab, which we’ll talk about. What’s not FDA or EMEA approved is cetuximab in triplet combination. But as an option, if you’re not giving a triplet regimen and you’re just doing a platinum doublet, you can give maintenance erlotinib after four to six cycles of therapy. That is an option based off of the SATURN trial.

And the bottom line was that there was a survival benefit. The hazard ratio was 0.87, but the P value barely made statistical significance at 0.044.

Okay, so what is the data for this? Well, cetuximab is an IgG1 chimerized antibody to EGFR.

And at the same time, there was a BMS-099 trial which was looking at carbo-paclitaxel with and without cetuximab. And the bottom line there was they both gave about a 1.2-month OS benefit. They both gave you a better response rate. But despite this data, the FDA did not approve cetuximab for use in metastatic non–small-cell carcinoma. So probably really hard to get approval or insurance coverage for cetuximab. But back in the day, I used to try.

And basically, the FLEX trial was conducted looking at the combination of cis-vinorelbine with cetuximab vs cis-vinorelbine alone in patients who had advanced disease and were chemo-naive.
And then progression-free survival didn’t actually look all that different. The triplet was 5.7 months vs the cis-gem, which was 5.5 months. And when we look at a subgroup analysis, it did trend towards favoring the triplet regimen.

Now, in this study, the response rate favored the triplet regimen.

But this is what really got the FDA to approve this, and this is the overall survival for the intent-to-treat population. The hazard ratio was 0.84 and the P value was statistically significant favoring the triplet regimen.
And so this was a phase 3 study done by Dr. Socinski. And so this was in chemo-naïve patients with a good PS and they were randomized to carbo and nab-paclitaxel vs carbo-paclitaxel alone.

**Nab-Paclitaxel**

- Cremophor (polyoxyethyleneated castor oil) may decrease efficacy and lead to hypersensitivity and neuropathy
- Nanoparticle-bound (nab) paclitaxel has been shown to be more efficacious than solvent-based paclitaxel in metastatic breast cancer
- nab-paclitaxel leverages the gp60/caveolin-1/SPARC transcytosis pathway to increase intratumoral drug concentrations

So what about some of the other drugs that we can use? So I mentioned before nab-paclitaxel. And this basically is a nanoparticle-bound paclitaxel. And it seems to be a little bit more efficacious because it doesn’t have Cremophor, which leads to hypersensitivity in patients who are taking other taxanes.

**Primary Endpoint Results**

**Objective Responses – ITT**

```
Percent Response

<table>
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<tr>
<th>Treatment</th>
<th>Response Rate</th>
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</thead>
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<tr>
<td>Nab-P/C</td>
<td>33%</td>
</tr>
<tr>
<td>P/C</td>
<td>25%</td>
</tr>
</tbody>
</table>
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Response Ratio = 1.31 (1.082 - 1.593)  
P = .005

Bottom line was response rate was better with the nab-paclitaxel arm.
And then when we look across the board at all histologic subtypes, the squamous cell carcinoma patients appear to really gain benefit from the nab-paclitaxel.

So this certainly lent some interesting data. I didn’t mention, but also in elderly patients it does appear that nab-paclitaxel may have very good efficacy, as well as in the squamous cell carcinoma patient population.

And then when we look at overall survival, there was a trend towards favoring the nab-paclitaxel arm, although it didn’t reach statistical significance.

And there is a phase 3 maintenance trial that is currently ongoing with the nab-paclitaxel.
That was a P value that was highly statistically significant. It was beneficial both in adenocarcinomas as well as squamous cell carcinoma patients.

And when we look at the overall survival, it was favoring the erlotinib maintenance. So this is certainly a reasonable strategy to go forward with in your squamous cell carcinoma patients if that is something that you decide to do.

And in this SATURN trial, out of 1,900 patients roughly, the hazard ratio favored progression-free survival with erlotinib maintenance.
Ok, so we can briefly just touch base for second-line therapy. Obviously, pembrolizumab—if you’re PD-L1-positive by immunohistochemistry—is now FDA approved. Also, there’s no biomarker associated with nivolumab for now and so that is also a viable option. There’s docetaxel-rumurimumab if you wanted to get some VEGFR inhibition into the patient. And then the older agents—docetaxel, erlotinib, pem—you wouldn’t use pemtrexed in squames, but in an adenosquamous patient you could consider it. I wouldn’t do it as second-line, but maybe further on down the line. And then gemcitabine.

**Dr. Socinski:** All right, if you can go to the next slide and we’re going to have a bit of discussion. I’m going to truncate the discussion a little bit because we’re getting along in time, and I’m a stickler for ending on time, so I won’t keep you over. But a couple of questions here. And actually, I’ll ask Ross to go to the other podium, since he’s the next speaker. And I guess this question would be a good question for Ross, and it has to do with KRAS. We didn’t talk about KRAS, but the question relates to the predictive value of KRAS in colon cancer with regard to anti-EGFR antibodies. And the same thing has not been seen in non–small-cell lung cancer. Any biologic reason for that?

**Dr. Camidge:** Well, bear in mind that KRAS mutations very rarely occur in squamous cancer, and most of the evidence of the EGFR antibodies is in spasm cancer, which I think is probably the dominant reason. It’s not as if the anti-EGFR antibodies are particularly effective in the general lung cancer population. I think one needs to emphasize that.

**Dr. Socinski:** And then, Anne, neci’s approved with cis-gem, right?

**Dr. Tsao:** Yes. So I give it with carbo-paclitaxel. I just find it a little bit easier to do.

**Dr. Socinski:** Do you give it with carbo-nab-paclitaxel?

**Dr. Tsao:** I have not done that yet.

**Dr. Socinski:** Okay, all right. We actually have a clinical trial looking at that in squamous, as that triplet combination. So that’s ongoing. But we’re just starting that.

**Dr. Rizvi:** Do you have a sense for why the hazard ratio for the women seems better than men? Is that just the sample size–related? In the necitumumab trial, SQUIRE? It seemed like the women did better. It’s like 0.63 vs 0.9.

**Dr. Socinski:** Yeah. So, I mean, we’ve known for a long time that female sex is a prognostic factor. I think it just kind of fits in with that. I don’t know that it’s necessarily had anything to do with neci, to be honest with you. But that’s that.

Other issues. Just, Anne, clarify on your case. One of the questions was when you presented the squamous case, your slide said that it was TTF1-positive. The question came in, isn’t that an adenocarcinoma marker?

**Dr. Tsao:** No, it’s not specific to adenocarcinoma. It’s actually specific to a thoracic malignancy, a lung cancer primary, or a thyroid. So that’s TTF1. It’s an immunohistochemistry that all our pathologists do to determine whether or not this is a primary lung cancer.

**Dr. Socinski:** Yeah, it’s more often much more highly positive in adenocarcinoma than squamous. But squamous can have a low rate. Yeah.

**Dr. Tsao:** It can be. Yeah, but usually, you know, it’s not uncommon to see it.

**Dr. Socinski:** Right. Yeah, in fact, Janet, did you have a [question]?
Dr. Camidge: So the way it works in terms of coverage is many insurers will defer to, for example, the NCCN guidelines, or if you can reference something which is in the public domain showing that it’s an actionable abnormality. So our own lab, even when the abstracts came out with BRAF V600E, we realized that this is something you could bill for in testing for lung cancer. So you have to have a pathologist who’s prepared to kind of, you know, roll as the data emerges. But yes, if you’ve already done all those things and then you suddenly decide that you want to do whole-exome sequencing, that’s probably not going to get covered.

Dr. Tsao: So usually, for all of our new patients, we have a 50-gene panel that’s soon to be a 250 panel, and we do that for all of the new patients. And we generally don’t have much pushback unless, as Ross mentioned, they’ve already had this testing done at home. And then it’s basically a fight.

Dr. Rizvi: I think the uptake has improved, though. I think that people understand the importance of this and I think one of the largest groups, UnitedHealthcare, recently did say that they will pay for foundation medicine type panels for lung cancer.

Dr. Tsao: One thing I’ve done to get around that is I’ll then send Guardant 360 for them, because it’s a blood-based test, if their insurance adamantly will not do genetic profiling from the tumor tissue.

Ms. Freeman-Daily: And you do that because it’s less expensive for them?

Dr. Tsao: Right.

Ms. Freeman-Daily: Good.
Management of a Patient With ALK+ Metastatic NSCLC Who Has Progressed on First-Line ALK-Targeted Therapy

D. Ross Camidge, MD, PhD
University of Colorado Cancer Center
Aurora, Colorado

Dr. Socinski: So, Ross, we have success in first line with our TKI of choice. Why don’t you talk about the perspectives in second line for ALK-positive disease?

Dr. Camidge: So you’ve got somebody who’s been on crizotinib and then it stops working. So here’s our case: a 54-year-old female, 10 pack year smoker, quit 20 years ago. She had a pneumonectomy, and then she had stage IV with recurrent disease about 2 years later. It was ALK-positive by immunohistochemistry. Remember, that’s an FDA-approved test now. Widespread disease, lymph nodes, liver, adrenals. Central nervous system was clear. Actually put on crizotinib with no dose reduction. She does great until about 11 months in. At that point in time, two things are happening at the same time: she’s getting headaches, but also her tumor markers are rising. And a PET scan you can see up there on the far right suddenly shows a right adrenal metastasis which has become PET-avid after a metabolic complete response in the middle. In addition, a repeat MRI of her brain now shows three new foci of CNS disease in the setting of a woman with a headache.

ALK+ Patients With CNS Disease Live a Long Time

<table>
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<tr>
<th>No. at risk</th>
<th>Months</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td>161 patients</td>
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</tbody>
</table>

- 90 ALK+ NSCLC with CNS mets
- Median OS from CNS mets = 49.8 mo
- Positive prognostic factors:
  - No extra-CNS mets
  - Good PS
  - No prior TKI

(Long enough to get WBRT side effects)


ALK patients live a long time, even with central nervous system disease. Once upon a time, as we go through medical school, you had lung cancer and it spread to your brain, your median survival was like 6 weeks. That is no longer true. This data, which we published in the JCO earlier this year looked at about 90 patients, showed that the median overall survival from the diagnosis of brain metastases was over 4 years. The reason that’s important is 4 years is long enough to manifest the side effects of whole-brain radiotherapy, most notably radiation dementia. And if you’ve never seen it, you don’t want to. It is singly the saddest thing I’ve ever seen, where somebody’s disease is controlled, but they are not in the conversation anymore. So my philosophy is do everything you can to avoid whole-brain radiotherapy, and I’m going to show you some of the ways we do that.
Okay, now one of the great things is in these next-generation drugs: ceritinib, alectinib, and to some extent brigatinib, and then there's another drug called lorlatinib—the last two are still not licensed—show activity in the brain. Not just are they better in the body, but they actually get into the brain, and enough gets into the brain to have activity against their disease that crizotinib is often not treating. And we're seeing response in the brain in the kind of 30%-50% range, and they're often prolonged. Again, if you look at some of these boxes here, you know, median duration of response is running 10 months, 18 months. Lorlatinib is the new kid on the block. That's often sold as a CNS penetrant ALK inhibitor, and we'll certainly see some data looking at that. But all of these are really CNS-penetrant ALK inhibitors.

So this is the second version of that flow sheet I showed you. This is when you have brain metastases developing or progressing on crizotinib. Now you have the same issue. It's not whether they're symptomatic or not. Really, here, if you have [less] than a certain number of lesions, often I will give stereotactic radiosurgery and keep you on the crizotinib. Exactly how many of the lesions are varies depending on where you are in the country or which country you're in. But when you have more than a certain number of regions, such that your radiation oncologist is saying, "Well, this is really a whole-brain radiotherapy situation," for me, that is the trigger to say it's time to go on to a next-generation ALK inhibitor to avoid having to give whole-brain radiotherapy.

Okay, in the first one, you could say, "Well, why don't I change when there are only two or three lesions I could give SRS to?" I guess it's conservatism. You know, I'm trying to milk out as much benefit from one drug which is still working in the body. But that's the only reason I have.
And, you know, I’m pleased to say we were completely wrong. And the reason is that even though we only see these what we call ALK-dominant mechanisms of resistance maybe in 35% of people, remember the response rate with the next-generation inhibitor post-crizotinib is 50%-70%. So there is clearly an ALK-dominant mechanism of resistance that we don’t yet understand, but that era in our understanding is working in our favor. So immediately post-crizotinib, there is no role to rebiopsy, because the vast majority of people are going to benefit from the next-generation inhibitors.

What about tolerability? Well, this is a table which I pulled together. With ceritinib, if you actually look in the second-hand column, the AEs are all great. I actually had to cap it at those which occurred at more than 30%, because the list for ceritinib was so long I couldn’t get them all in there. 62% of people on the starting dose of ceritinib need a dose reduction. It is not well tolerated in the majority of people. It can be, but not in the majority.

Alectinib was the initial reports in presentations just yesterday, about a 10% dose reduction rate in the product label. It’s now running about 24%. Brigatinib, we’ll see some data in terms of what they’re proposing to take forward with their dose. That’s probably got about a 20% dose reduction rate. Lorlatinib, we haven’t really seen data, because it’s still in the phase 1. In terms of the side effects that you see, mostly gastrointestinal side effects with ceritinib, a lot of upper-GI side effects: nausea, vomiting, some diarrhea. You get that to some extent with the others, alectinib particularly. About 30% get constipation. You get some edema, and it does have a photosensitive skin rash. People will get sunburned very quickly on alectinib. So you have to warn them about using sunscreen.

Brigatinib has a slightly funny side effect. About 3% of people within the first literally couple of days of going on the drug will develop some hypoxia. They can actually push through it and then be fine later. 97% of people aren’t getting that. So it happened early on in there. We seem to manage it. Lorlatinib has hypercholesterolemia, hypertriglyceridemia, some word-finding difficulties, and some edema issues. But that’s still a work in progress, as those abstracts will tell you.

### Not One Next-Generation Drug for All Patients?

- Alectinib-acquired resistance clinical specimen/cell line (MGH056)—I1171T

<table>
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<th>Drug</th>
<th>Common AEs All Grades</th>
<th>Grade 3/4 AEs (≥5%)</th>
<th>Source</th>
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<td>Diarrhea (8%), nausea (65%), vomiting (52%), ALT increase (44%), fatigue (43%), abdo pain (30%)...</td>
<td>ALT increase (30%), AST increase (15%), lipase increase (6%), diarhea (6%), nausea (6%), hyperglycemia (6%), al phs increase (6%), fatigue (5%), anemia (5%)</td>
<td>Felip et al. 2014</td>
</tr>
<tr>
<td>Alectinib phase 2</td>
<td>Myalgia (17%), constipation (10%), fatigue (14%), edema (9%), rash (9%), photosensitivity (9%)</td>
<td>None</td>
<td>Ou et al., ASCO 2016</td>
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<tr>
<td>Brigatinib phase 2</td>
<td>Nausea (40%), diarrhea (38%), cough (34%), headache (27%), fatigue (27%)</td>
<td>None</td>
<td>Kim et al. Abstract 9007, ASCO 2016</td>
</tr>
<tr>
<td>PF00439222 (lorlatinib)</td>
<td>Hypercholesterolemia (58%)</td>
<td>Hypercholesterolemia (5%-7%) Note: nil to moderate speech, memory, mood effects seen in some!</td>
<td>Solomon et al. Abstract 9000, ASCO 2016</td>
</tr>
</tbody>
</table>

Post-using one next-generation inhibitor, suddenly you can use anything—that model breaks down, because what emerges is, whilst you’re covering most of the resistance mechanisms, every single one of the next-generation ALK inhibitors has an Achilles’ heel. But they have different Achilles’ heels. So here, this was a patient who had responded and then progressed on crizotinib, and then responded and then progressed on alectinib. Rebiopsy showed that they had a specific resistance mutation called I1171T, which in cell lines was resistant, not surprisingly, to crizotinib and alectinib, but sensitive to ceritinib. And so the Mass General group rechallenged this patient, or challenged this patient with ceritinib after alectinib, and they responded. So a very personalized approach now emerging in the third-line ALK inhibitor setting.
At this year’s ASCO, we also saw that brigatinib, probably the next drug to be licensed, is also showing activity against G1202R. So we’re going to have more than one option.

Second-Generation Followed by Different “2nd/3rd”-Generation ALK TKI

- PF-06463922 (NCT01970865)
- AP26113 (Planned. PI: Stinchcombe) 180 mg

There are some studies that are actually formally exploring this post-next-generation TKI. One is with lorlatinib—that’s what 03922 is—and AP26113 is brigatinib, and that’s an investigator-initiated trial led by Tom Stinchcombe, who was at University of North Carolina, has now announced that he’s moving to Duke, all the way down the road.

Dr. Socinski: All right, Anne, we’re going to ask you to come back to the podium and address this issue. I’ll ask you a question about neci in a second. But one of the questions was, “What is necitumumab approved with?” It’s actually approved with cisplatin and gemcitabine. We don’t have any other things. But just the tolerability of necitumumab. I find it similar to cetuximab.

One of the problem childs is this mutation called G1202R, which many of them are resistant to. Lorlatinib, that one which is still in phase 1 studies, is clearly showing activity in G1202R. Those studies are still going on.
**Dr. Tsao:** It's pretty close to cetuximab. There is some speculation that maybe you get a little bit more rash, but I haven't really seen that.

**Dr. Socinski:** Except in the hypersensitivity belt. Since it’s fully humanized, you have lower hypersensitivity reactions.

**Dr. Tsao:** Right. I wasn’t on the East Coast, so I didn’t ever see it with cetuximab, either.

**Dr. Socinski:** Yeah, yeah. We saw it all the time in North Carolina. All right, talk to us about EGFR-resistant disease.
Management of a Patient With EGFR+ Metastatic NSCLC Who Has Progressed on First-Line EGFR TKI

Anne S. Tsao, MD
The University of Texas MD Anderson Cancer Center
Houston, Texas

Case 6

- 47-year-old Asian male patient presented with cough, SOB, and a 5-pound weight loss. A PET-CT scan showed multiple bilateral pulmonary nodules, multiple bone metastases. Brain MRI is negative.
- A biopsy of one of the pulmonary nodules shows adenocarcinoma that is cytokeratin and TTF1 positive.
- Genetic profiling shows EGFR mutation positive for L858.
- Patient was started on erlotinib and did well for 16 months with a partial response.
- His restaging studies show significant disease regrowth with multiple pulmonary nodules increasing in size.
- A repeat biopsy of the largest growing pulmonary nodule shows EGFR mutations L858 and also T790M.

Dr. Tsao: Okay. So this was a 47-year-old Asian male and he again presented with cough, shortness of breath, and weight loss. And his initial PET-CT scan showed multiple bilateral pulmonary nodules and multiple bone mets. Brain MRI was luckily negative. And a biopsy showed it was adenocarcinoma, and the genetic profiling showed an L858 EGFR mutation. So he got erlotinib, and he did great for 16 months with a partial response. But then he began having disease regrowth with multiple pulmonary nodules increasing in size. So we then went and got another repeat biopsy of the largest-growing pulmonary nodule, which showed the L858 mutation, but also now a new T790M mutation.

So when an EGFR-mutant patient progresses, the progression is not the same. You can get oligo-progression. So, very briefly, if you get oligo-progressive disease—meaning you only have one site that appears to be growing—we often will use local control (whether by radiation therapy or surgical resection) to get rid of that one site, as long as everything else is controlled and you keep them on the original drug that you had them on. There are several studies that have shown that you can give them additional progression-free survival benefit anywhere between 6 to 10 months. There was one case report of 41 months for overall survival by using this strategy.

But we see this both for the EGFR mutation patients and also with the ALK mutation patients. So I think it’s general practice that if you have a solitary lesion that grows, you’d usually take care of it and keep them on the original therapy.
But what happens when they have global progression? And this is like my case. Well, so, in those patients who you probably have to change treatment of therapy, one thing I want to caution is that EGFR-mutant patients will get a flare of their disease if you take them off the EGFR TKI.

And you'll see in all of our clinical trials in EGFR mutation patients that we only allow a short-window washout period of only a couple to a few days. And that’s because we all believe that this EGFR mutation flare can happen. And then those patients may become so ill very rapidly that you can’t treat them with their salvage therapy. Now, in your patient who has got global resistance, in the past, we used to do chemo or chemo followed by one of the first-generation EGFR TKIs. We previously did do chemo plus EGFR TKI at the same time or intercalated it. And there were trials that suggested that these were all safe.

But there was a recent trial called IMRPESS, which I don't have time to go into, where we no longer advocate giving chemo plus an EGFR TKI together after a patient has progressed on an EGFR TKI. So if you wanted to sequence them, you could do that. There are still some people that believe intercalating the drug works, but generally right now, don’t give it concurrent with your chemo after they have progressed on your EGFR TKI.
So what about osimertinib? So this is a drug that just recently got FDA approval, and the prior name was AZD9291, but the new name is osimertinib.

And you can see from the waterfall plot that this was quite impressive for the patients, with a very good response rate of about 51%. And this was in the overall population.

Now, when you broke it down and you specifically looked at the T790 mutation, the response rate was 61%. So again, very favorable.

And so this was an early-stage study looking at patients with an EGFR mutation who had progressed after a front-line EGFR TKI.
If you look at it in terms of those who had no T790M picked up, the response rate went down to about 21%. So the indication for osimertinib is in the T790 population. It’s unclear whether these patients may have not just had the T790 picked up, because the tumor can be very heterogeneous. But, you know, there is another thought that this drug may actually work still in those that you haven’t identified their mechanism of resistance.

Now, in terms of toxicity, there’s always a cost with all of these drugs. Luckily, this drug doesn’t give you as much diarrhea as the other EGFR TKIs, so diarrhea and rash are down more. And also, this doesn’t give you hyperglycemia, which is something that one of the other drugs that had been under development in this space actually did give. But you do have to watch out for things like QTc prolongation, so you do have to change your practice by looking at some EKGs. And certainly, there is always a risk of having a slight amount of diarrhea, but certainly nothing like the other EGFR TKIs.

So the FDA did grant accelerated approval to this agent on November 2015. The patients have to have progressed on the prior EGFR TKI, and the T790M—right now, at least—has to be confirmed in tumor specimens although recently, as all of you know, the FDA did approve a blood test for EGFR mutation. So we’ll see if this changes. The dosing is 80 mg/day with or without food.

There is a study in the front-line setting called AURA 3 and this, again, is for EGFR mutation–positive patients. And this is, again, looking at a comparison with chemotherapy.
Now, obviously, we always worry about resistance, and so this was a case study that was reported looking at a patient treated with osimertinib and they did detect a new mutation, C797S, that occurred after that. Now, the interesting thing about this is that this patient became sensitive again to the gefitinib, and so we may be coming all the way back around, depending on the typical mutation or the type of mutation that occurs after the treatment with these drugs. So I wouldn’t write off any oral TKIs at this point in time for lung cancer.

But certainly, there are other pathways of resistance that are being looking at, and that being one of them. Also, you have to look for small-cell transformation. I have seen that happen, and so it’s definitely something you watch out for. And then certainly, alternate upregulated pathways. I had an EGFR mutant patient who was resistant, when rebiopsied was found to be ALK positive and then responded subsequently to crizotinib. So these are all things that you have to consider now, but the bottom line is, you must rebiopsy the patients after they have progressed off of their EGFR tyrosine kinase inhibitor.

Okay, so for practice right now, if you’ve got oligo-progression of an EGFR-mutated patient, you continue their original EGFR TKI and just do local therapy—usually SBRT, radiation, in rare cases surgical resection. If they have global progression, you must test them with a rebiopsy. And if they are T790M, you can give them osimertinib. If not, then usually chemotherapy or chemotherapy followed by an EGFR TKI is what you can do off protocol.
And so this is just a very short algorithm about how adenocarcinoma of the lung is rapidly evolving. It isn’t just one disease anymore—it is now at least 20 different diseases. I’m only listing some of the more common mutations that have been reported. But certainly, there have also been other pathways that have been noted—PARP being one of them, although PARP tends to now be looked at more in small-cell lung cancer, and also in breast cancer. But there have been some trials in metastatic squamous cell carcinoma of the lung using PARP inhibition with a platinum doublet, and then also concurrent, for stage III, with concurrent chemoradiation therapy.

**Dr. Socinski**: So just one quick question for Anne before we let Naiyer take us home with the immune checkpoint blockade talk. Is osimertinib not effective in other mutations other than T790M? So I think it’s important to realize that this also inhibits the native mutations, the exon 19. So any other sensitivity mutation it should inhibit. But the problem with the first-/second-generation, at least at clinically achievable doses, they won’t inhibit the T790M, and that’s the beauty of osimertinib. Would you agree with that, Anne?

**Dr. Tsao**: Absolutely. Yeah.

**Dr. Socinski**: Thank you. There’s a question about the flare thing. So if you stop the TKI before you get that new drug…

**Dr. Tsao**: Just give them some EGFR inhibition. So if, for whatever reason, they forget their medication or they forget your instructions, and they flare with disease, put them right back on the original and see if you can contain it, at least until you can get them the osimertinib.

**Dr. Socinski**: Okay. Now let’s hear about your case.

**Dr. Rizvi**: So one more comment. I can be noisy now. So given the data with afatinib and cetuximab being active in EGFR-mutant lung cancer with acquired resistance, is there any sort of appetite to look at 9291 with cetuximab? I mean, the skin tox is a big issue with afatinib. So maybe a more potent EGFR TKI with cetuximab could be active in T790M-negative. Anyone doing that?

**Dr. Camidge**: Yeah. So AstraZeneca and Lilly are planning a combination study together to look exactly at that.
Dr. Rizvi: So, this is a 62-year-old man, this patient of mine, who has KRAS-mutant lung adenocarcinoma of the right upper lobe. He has mediastinal lymph nodes as well as bone metastases, brain metastases. His past history is relevant for a substantial smoking history, stopped 32 years ago. He has a history of rheumatoid arthritis, psoriasis, as well as a cutaneous T-cell lymphoma. I’m not making this up. He really does have these things.

And he underwent treatment with Gamma Knife to four brain metastases, and then received pemetrexed and carboplatin with initially some tumor regression after two cycles. But after four cycles he’s had progression of pain in his iliac lesion with quite significant sciatic symptoms, and he underwent radiation to his right iliac lesion. In addition to his KRAS positivity, we did do a PD-L1 test on him using the 22C3 clone, and he was deemed to be negative with a proportion score of 30%. So, just to sum up: KRAS mutant, prior smoker, history of psoriasis, rheumatoid arthritis, progressed after first-line chemotherapy.

Dr. Rizvi: So, this is a 62-year-old man, this patient of mine, who has KRAS-mutant lung adenocarcinoma of the right upper lobe. He has mediastinal lymph nodes as well as bone metastases, brain metastases. His past history is relevant for a substantial smoking history, stopped 32 years ago. He has a history of rheumatoid arthritis, psoriasis, as well as a cutaneous T-cell lymphoma. I’m not making this up. He really does have these things.
The issues of this rheumatoid arthritis and psoriasis, I think, are relevant when we’re using immunotherapies. Typically, psoriasis or vitiligo or less significant autoimmune disorder histories were excluded from all of our clinical trials that we were doing with PD-1 therapy. So we really don’t have much experience.

The feeling is that, because they have an autoimmune history such as ulcerative colitis or something there that is at risk of being exacerbated. There actually is a poster at this meeting in melanoma with patients that were treated with various autoimmune conditions, and about a third of them did have some flare of their disease. And the GI ulcerative colitis, Crohn’s, was more than some of the other ones.

So there certainly is some risk involved. I think it’s a matter of assessing the situation with your patient, weighing the pros and cons. The PD-L1 test can be helpful to you; if they’re more positive, then maybe it’s worth the risk. And also the activity of the disease—he really has had a history of it, but doesn’t have any active rheumatoid arthritis and so I think that our fear was a little bit lower.

**Dr. Socinski:** And you have to balance that against his active lung cancer, right?

**Dr. Rizvi:** Right, absolutely. He’s got aggressive lung cancer. That’s right.

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**Case 8**

- 53-year-old man with squamous lung cancer
- Past history: former smoker 10 pack year otherwise negative
- Diagnosed July 2015 with T2N2M0 disease
  - Treated with cisplatin, etoposide, and concurrent RT followed by right pneumonectomy, Nov 2015
  - Pathologic stage T3N2, >90% viable tumor, positive bronchial margins (R1 resection)
- Mediastinal recurrence Jan 2016 with unrelenting cough

The second case—these are both cases that I recently have been treating—he’s a squamous-cell lung cancer. He’s a former 10 pack year smoker. He underwent resection of a locally advanced lung cancer after chemo and RT. He had a bad-acting cancer with most of the tumor being viable at resection despite the chemo and RT, and his margins were positive as well. He recurred in January of 2016—so a very short time after—and with a mediastinal lymph node and with significant cough symptoms. And he came to see me at that point.

**Case 8 (Cont’d)**

And he was biopsy-proven for recurrence. Again, these scans don’t really make out the extent of disease, but he basically was PD-L1 strongly positive—80% positive—and he was treated with pembro for four cycles and had a complete radiologic response with no evidence of cancer. And I think that that’s also a situation we have to think about a lot, and it would be interesting to hear my colleagues’ take on how long we continue these therapies. He’s got only one lymph node area of recurrence. He’s had a complete response after four cycles of therapy. Are we going to give this guy PD-1 for the rest of his life, or have we potentially cured this patient? So I think that’s something that we can talk about afterwards.

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**CheckMate 017 and 057**

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Update from ASCO 2014:
- CheckMate-057: 2-year OS rate in nonsquamous NSCLC was 29% with nivolumab vs 16% with docetaxel
- CheckMate-017: 2-year OS rate in squamous NSCLC was 33% with nivolumab vs 21% with docetaxel

So the trials that led to approval of nivolumab last year for second-line therapy for lung cancer were 017 and 057. 017 is the squamous trial, only squamous, and the 057 was nonsquamous patients. And they’re both randomizing patients to nivolumab vs docetaxel. The overall response rate was clearly better in both vs docetaxel: 20% vs 9% and 19% vs 12% in the squamous and nonsquamous trials. The PFS in the squamous patients was a little bit better, 3.5 vs 2.8 months, whereas in 057 it actually was worse. And I think that’s one of the challenges that we have to contend with immunotherapy, where the PFS sometimes does not reflect the aggregate benefit of these therapies, because the overall survival was clearly better in both. And I think that comes into the biomarker story. I think there is a proportion of patients with lung cancer who particularly have deep and durable benefit that tend to carry the overall survival which was why the PFS is a bit of a tricky endpoint in unselected patients.

The PD-L1 expression, I think, has been a bit of a quagmire in terms of interpreting these data, because there’s all sorts of scores that you have to contend with in terms of the different clones, from BMS using one clone and then Merck using another one and now Roche using a third one. The cutoffs are different—the Roche assay for bladder cancer uses only immune cells and doesn’t use tumor cells. So I think it’s a challenging space to get your head around. I think for lung cancer, and for most cancers, the bottom line is that the more positive you are, the more likely you are to respond to these therapies. And I think the cutoffs are more relevant in the first-line space in lung cancer, which we’ll talk about in a bit.

Nevertheless, the response rates in 017 really weren’t any different based on PD-L1 expression. But if you look at the overall survival, it did seem to favor a little bit those patients that had higher PD-L1 expression did better in terms of OS. Whereas in 057, it was clearly a substantial increase in response rate, from 9% to 37%, and then the overall survival went from 10 months to 19.4 months. So it’s a bit of a scenario where if you have no expression of PD-L1, then you’re probably likely to do comparable to chemotherapy. So I think that’s really room for us to do better.

The KEYNOTE-010 was also read out last year. This was actually a follow-on to KEYNOTE-1, which was a phase 1 trial of 495 patients with lung cancer—everyone had new tumor biopsies. And the subset of those patients with this assay having more than 50% expression had a response rate in the 40%-plus range. And this led to accelerated approval in that subset of lung cancer that had more than 50% expression.

And now, the KEYNOTE-010 is out. We saw again the correlation with PD-L1 expression and response rate. The comparator in this first randomized trial with pembrolizumab was docetaxel. And you can see that the PD-L1 of more than 1%—which is about three-quarters of patients with lung cancer who have at least 1% PD-L1 expression—the response rate was 18%. If [PD-L1] was more than 50%, [the response rate] was 30%, which clearly beat chemotherapy in terms of overall survival in particular.

The PFS, again, is a bit tricky. If you take the more than 1%, it’s about the same. Again, I think that the high-positive patients are those that benefit the best to single-agent therapy.
So we have clearly nivo-approved, second-line therapy for all-comers. Pembro is approved in the high-positive patients. That could change potentially based on the KEYNOTE-010 data, which is showing activity in the intermediate subgroups.

What about the first-line space? And these data also additionally have been updated at ASCO of this year. But if you have high expression, the overall response rate is 50% and the median overall survival has not [been] reached. And as of this ASCO, it’s also been not reached. So some of these patients in the first-line space can really do remarkably well with single-agent therapy. And nivolumab, as well, for those patients that have high-positive expression, do particularly well.

Finally, POPLAR data was also published last year, and atezolizumab has been submitted for an accelerated approval path. This trial was randomizing atezolizumab—which is a PD-L1 antibody—vs chemotherapy. And again, the survival benefit was superior, 12.6 vs 9.7 months. And I think the story with POPLAR is really interesting, because when it first read out at ASCO of last year, it actually did not meet the statistically significant endpoint of overall survival. But as the data matured and it was cut again at ESMO, it actually did meet statistical significance. And when you look at the curves, they actually start together and they separate and they continue to separate, suggesting that for immunotherapy, some of these patients don’t need to have a dramatic response to these treatments. They can have slow and modest tumor regressions, and actually regressions over time. So with immunotherapy, stable disease can be a good thing for some of our patients. But again, with this trial as well, PFS was inferior but OS was clearly superior.

So both pembrolizumab and nivolumab have trials: pembro with KEYNOTE-024 and nivolumab with CheckMate 026. They’re both, to my understanding, expected to read out by ESMO of this year. They’re both first-line randomized trials in PD-L1–positive disease to PD-1 therapy or first-line chemotherapy. And so for those high-positive patients, my impression is going to be that if you’re those 25% of lung cancer that have really high PD-L1 expression, I think it’s likely that these drugs are going to beat chemotherapy and will be a new standard, potentially based on those data. So I think that PD-L1 testing will be more a part of our standard SOP as we have the first-line space where it’s more important, I think, to be PD-L1 positive. And these just show the first-line trials that are not just the CheckMate-026 and -024, but there’s also a second pembrolizumab trial. There’s also atezolizumab trials, also both vs chemotherapy, in the first-line space.
There are other issues in terms of exclusion from the immunotherapy trials, and the other ones are hepatitis B and C and HIV. And so those are also scenarios that come up clinically, and we don't really know what to do. In general, those patients are probably okay to treat. There are trials in hepatocellular carcinoma, for example, where patients do have hepatitis B or C as part of their HCC, and they actually don't flare in terms of their hepatitis. So I think that prior RT and pneumonitis in the past—and rheumatoid arthritis, autoimmune stuff, hepatitis—are all kind of relative contraindications, they aren't absolute contraindications.

So what is the only absolute contraindication to getting PD-1 therapy that you can think of? I ask this quite a bit, and people don't get it right. Absolute contraindication. You can yell it out. What's that?

**Participant:** He wants special treatment.

**Dr. Rizvi:** Right. Right here.

**Participant:** Organ transplant.

**Dr. Rizvi:** Organ transplant. So if you have had a prior liver transplant, heart transplant, or lung transplant, those are absolute contraindications. There actually was a letter in the New England Journal a couple of months back of a case of a liver transplant case which did get rejected with immunotherapy. It makes sense that you would reject these organs. And you could do it if they had a kidney transplant, because you can always dialyze them. But it's kind of hard to live without a heart, so don't do that.

**Dr. Socinski:** So, Naiyer, one of the questions here is, “Are there differences between pembrolizumab and nivolumab?” Are they Coke and Pepsi?

**Dr. Rizvi:** Yeah, I think so. I mean, I think that if you look at the—you know, there are some—I think that in terms, if you look at the efficacy numbers for pembrolizumab, nivolumab, as well as atezolizumab, they seem to have very similar response rates, very similar overall survival. So I think the differences might be just the schedule: nivolumab given every 2 weeks, pembrolizumab given every 3 weeks. So I think I would say yes.

**Dr. Socinski:** And then “What percentage of patients fall into that greater than 50% proportion score?”

**Dr. Rizvi:** So the prevalence of high positivity is about a quarter of patients.

**Dr. Socinski:** And then one of the questions relates to the biomarker testing, and it's a question you and your patient chose. I assume that was the companion diagnostic test that was there. Is that an appropriate test to use to make decisions about nivolumab? Or would you use it? Would you even test for nivolumab?

**Dr. Rizvi:** Yeah, so I think that pretty much everyone who has non–small-cell lung cancer should get PD-1 therapy at some point. And I think that the assay, for me, is of some use for making decisions such as the patient who has maybe some autoimmune history. The other situation is if you have somebody who is on chemotherapy and maybe has a 10% increase in the tumor size, it's not truly reached its progression, but you see them eking in the wrong direction. Before PD-1, you might just keep them on the chemotherapy because it may be a bit of a blip. But now, if you knew that they were 100% positive vs 0% positive, you may be more likely to switch therapies earlier. So I think it's just another tool in terms of helping you think through your patient. But I think that irrespective of it, we see activity in negatives, including 0% positive patients. That patient that I mentioned with the 20%, 30% positivity, he responded. So, I mean, it's just a guide, I think, more than an absolute biomarker.

**Ms. Freeman-Daily:** Isn't there some indication that those of us who have driver mutations tend to be less likely to respond?

**Dr. Rizvi:** Right, that's a great point. So we do know that the patients that have the best response to these treatments are those tumors that are most genetically damaged. And so those are tumors that are from smoking, carcinogen, from UV light exposure, for chronic viral infections where the virus, on a chronic basis, induces genetic instability. So for our patients who have lung cancer with driver oncogenes—such as EGFR, ALK, RET, ROS1—most of those patients are never-smokers. And for the never-smokers, the response rate is far less with immunotherapy than those patients who have had tobacco carcinogen-induced lung cancers.

What was a little bit encouraging, though, is the data that was presented at this meeting looking at combination immunotherapy with ipilimumab and nivolumab. It seems to be very active. It's more active than single-agent. There are more toxicities. But in the small numbers of patients who were part of that sort of exploratory trial, those that had EGFR mutations or never-smokers, there actually was some reasonable activity. So it could be that driving the immune system harder with combination immunotherapy could be a better opportunity for those patients who are never-smokers with driver oncogenes.
NSCLC Forum: Bringing the Patient to the Foreground of Evidence-Based Lung Cancer Care

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