MED-IQ

Advanced Non-Small Cell Lung Cancer Community of Practice Audioconference

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MODERATOR: Welcome to the Advanced Non-Small Cell Lung Cancer Community of Practice Audioconference with faculty expert Dr. Mark A. Socinski. This activity is sponsored by Med-ID. I'm Olivia, your moderator for today’s discussion. This audioconference is being recorded; however, resale of the content is prohibited. During today’s call, you will have an opportunity to discuss methods for overcoming practice-related barriers in the management of advanced non-small cell lung cancer (NSCLC) and draw on faculty expertise to help maximize patient outcomes and satisfaction. This unique platform provides the opportunity to ask your most pressing clinical questions related to the management of patients with advanced NSCLC and receive insight directly from Dr. Socinski. This activity has been developed as part of the complementary PI CME initiative, Performance Improvement Strategies in Advanced Non-Small Cell Lung Cancer, for which Dr. Socinski has served as faculty. Additional details about this initiative will be discussed during today’s audioconference.

I am pleased to now introduce today’s faculty speaker. Dr. Mark A. Socinski is Visiting Professor of Medicine in Thoracic Surgery, Director of the Lung Cancer section within the Division of Hematology/Oncology, as well as the Co-Director of the UPMC Lung Cancer Center of Excellence and Co-Director of the Lung and Thoracic Malignancies Program at the University of Pittsburgh in Pittsburgh, Pennsylvania. Let’s begin, Dr. Socinski.

MARK A. SOCINSKI, MD: Good evening, and welcome to this Community of Practice Audioconference for Advanced Non-Small Cell Lung Cancer. The goal of this call is to bring together specialists who are interested in the care of patients with advanced NSCLC to discuss current challenges and advances in the care of these patients. Before I open it up to your questions, first I want to share some of the reasons why programs such as this, our performance improvement initiative, are so important and provide you with a bit of insight about the current state of NSCLC care.

For those of you who may not be familiar with performance improvement or PI programs, this is an AMA-approved CME format in which clinicians work on improving their

individual performance by completing two stages of retrospective patient data collection and implementing a plan for improvement into practice. There is an increasing understanding that improving care will require us as clinicians to measure and monitor indicators of quality with the goal of identifying areas in which current practice falls below established standards and where opportunities for improvement are present. PI CME is one method to do this.

In this program, there are three phases to the practice, and five CME credits are available for each step with an additional five credits available to clinicians who complete the entire activity for a total of 20 credits.

In the first step or Stage A, participants perform a retrospective analysis of 10 patient charts by completing a standardized data collection form for each chart. The data can either be entered online directly by the participant or the designee, or faxed to Med-IQ and one of their staff will enter the data for you. Once the chart review has been completed, participants receive a summary of their practice patterns relative to those of their peers enrolled in the program and national standards when available.

In the next step or Stage B of the program, participants review these results and design process-based improvement strategies specific to the needs of their practice. To help develop a plan, clinicians may read a CME-certified implementation guide that outlines the current evidence base and provides practical tools and resources to help clinicians meet the performance measures. I recommend that participants implement their improvement plan for at least 30 days before returning to review an additional 10 patient charts in the final stage or Stage C in the program. The charts selected for this stage of the program should be for patients who were seen after you started the program.

At the conclusion of Stage C, participants receive a summary of their current practice patterns relative to their earlier practice patterns as well as those of their peers and national standards, and they can assess whether there’s been any change in their practice. Clinicians can see improvements in their practice or areas where additional improvement is still needed.

So now that we’ve discussed the framework of PI CME, I’d like to take a few minutes to highlight some of the key challenges in managing advanced NSCLC, specifically the

role of histology in determining optimal treatment strategies for advanced NSCLC as it relates to median survivals, toxicities, and testing for EGFR mutations; new thinking about classification of adenocarcinomas; and certainly the emerging world of genetic mutations as biomarkers of response and for treatment selection for advanced NSCLC. And this largely relates to the importance of testing for certain genotypes such as EGFR or ALK, and we can talk about ASCO and NCCN positions on genetic testing of the sort. Another area is maintenance therapies in advanced NSCLC—how they influence progression-free survival and overall survival; we'll also look at guideline recommendations with regards to maintenance therapy.

I would like to now open it up to comments and questions about challenges that you face in advanced NSCLC care and/or strategies for improving the management of patients with this disease. We can begin with one or two questions we received in advance by e-mail, but please feel free to let the operator know if you have a question you'd like to address this evening.

MODERATOR: Thank you, doctor. At this time we will begin the question and answer session. To ask a question, please press 0 followed by a 1 on your touchtone phone. Questions will be answered in the order they are received. Again, you may ask a question by pressing 0-1 now. Please pause with us to see whether we receive any questions in cue. And while we pause, Med-IQ did receive several questions in advance for this audioconference. At this time, Dr. Bo Geist will share a question that was submitted by one of your colleagues.

DR. GEIST: Thank you. One of the questions submitted by the participants registered for this call asked about maintenance therapy or maintenance treatments particularly for patients who may have achieved pathologic complete response. So Dr. Socinski, if you could address that, what do you think about a patient in this particular situation, someone who has achieved pathologic complete response (CR)?

DR. SOCINSKI: It's a good question. Unfortunately you've got a rather complicated answer in my opinion, and I'll tell you what the data show. Certainly in the US right now we have two agents that are approved for maintenance therapy. One is pemetrexed; remember that approval is restricted to nonsquamous histology. The second drug is erlotinib, based

on the results of the SATURN trial. So let’s say you give a patient four cycles of a platinum-based doublet, and they have stable disease versus a very good response or perhaps a CR, which is unusual but we do see it occasionally. Now the data with erlotinib showed a survival benefit only in patients who had stable disease and did not show a survival benefit in patients who had robust response with either partial responses (PRs) or CRs. And in fact when erlotinib was approved as a maintenance drug in Europe, the language for the approval in Europe says to use this for maintenance only in patients who have stable disease, suggesting that if you have a CR or PR, that you could give the patient a treatment break and that maintenance was not known to be beneficial.

Now if you look at the pemetrexed data, whether you look at switch pemetrexed or continuation pemetrexed, interestingly in the nonsquamous populations, the benefits from maintenance pemetrexed seemed to be there whether you had stable disease or responsive disease. So in that setting, induction response did not seem to make a difference with regard to benefit of maintenance pemetrexed.

So having said that, I do think that whether or not to use maintenance therapy in patients who have very good responses and certainly CRs is a judgment call. In general those patients have a very minimal disease state; they typically don’t have threatening disease in terms of the likelihood that their cancer is going to cause them to be symptomatic or will lead to a mortality event over the next couple of months. For those patients, I often think about giving them a treatment break. I think conversely in those patients who have stable disease. Now remember “stable disease” describes a spectrum of patients. It is patients who actually have a little bit of progression, but by RECIST criteria don’t satisfy that 20% worsening to be called progressive disease. Many of those patients with stable disease are actually slowly getting worse, and if you stop treatment or don’t pursue maintenance, they’re at risk of having disease-related complications that may preclude them from getting further therapy down the road, for instance second-line therapy. So in those patients with stable disease, data suggest to me that first-line therapy doesn’t really have a big impact, and you should probably think about maintenance therapy. Personally, I might call this early second-line therapy, but we’ve now used the term maintenance therapy in this setting. I would strongly think about maintenance therapy in those patients who have stable

disease because I think that you may miss an opportunity to treat them if they have a disease-related complication that rapidly erodes their performance status in a few months or so.

MODERATOR: Thank you. And again a reminder to our participants, you may ask a question by pressing 0-1. Dr. Geist, I'd like to turn the audioconference back to you for additional questions.

DR. GEIST: Certainly. Thank you Dr. Socinski for that well-thought-out and thorough response. We have several other questions here. The one I'd like to get to next is regarding ROS1 testing. One of our participants wants to know, given the fact that this rearrangement occurs in approximately 2% of adenocarcinoma NSCLC patients, what's your position on the feasibility of testing for that?

DR. SOCINSKI: Good question, and I think we don't really know the percentage of ROS1 translocations, but I might even argue that 2% may be a little high. So what should be your strategy when you're managing patients and you have these very uncommon genotypes such as ROS1?

Just for those of you who may not be familiar with ROS1, it is an oncogene as a result of a translocation. It shares about 50% homology with ALK, and in fact if you look at the kinase domain of ROS1, the homology is closer to 80% in that population. So crizotinib works well in ALK-translocated patients, and crizotinib seems to work as well in ROS1 patients. So the reason to think about ROS is because crizotinib is a really good drug that's really targeted for these patients. When you have a targeted agent that targets a specific genotype and has a very dramatic result, you would not want to miss the opportunity to treat a patient like that.

So how do you identify them? Now if you look at the data from the Lung Cancer Mutation Consortium—for those of you not familiar with the Lung Cancer Mutation Consortium, the goal was to fully genotype 1,000 lung adenocarcinomas—their current data show that about 25% of patients have KRAS mutations, about 17% have EGFR mutations, and about 7% have ALK translocations. That's 50% of the patients who have one of those findings, and there was virtually no overlap, so if you have one of those findings, you shouldn't go testing for ROS1. However, if EGFR and KRAS are wild-type and ALK is negative, I would seriously try to get a patient tested for ROS1. Let me tell you about the demographics of the

population. They're very much like the ALK population, they're younger patients, they're equally men versus women, they're almost always adenocarcinoma, and they're almost always never/light smokers. So particularly in a younger patient, never/light smoker with adenocarcinoma who was again wild-type on all the other ones, I would clearly try to get a ROS1 FISH test done because crizotinib could be a very impactful drug for those patients.

I think if technology evolves, it's going to be easier to do concurrent multiple tests so ROS1 will be integrated into many platforms in terms of next-gen sequencing and their sort of approaches, so I think over time it's going to be easier and easier to get this particular test done. But I would think about it right now in the so-called triple negative lung cancer patients—EGFR, ALK, and KRAS negative.

MODERATOR: Thank you. And Dr. Geist, please continue with another question.

DR. GEIST: Absolutely. Dr. Socinski, what are your thoughts on the minimum requirements or the minimum standard of molecular testing in standard practice in particular? Would you do EGFR only, EGFR and KRAS, or would you do ALK or...

DR. SOCINSKI: Yeah, I think that's... there's not one... I'll give you a couple of thoughts here. I'll give you my advice first. I think we should be testing for all of these at the same time. And it makes it quicker. One of the things that's difficult is that the testing usually takes a good week or 2 once you have adequate tissue, and therefore if you were to do the sequential test, let's say you were going to test for KRAS first and then test for EGFR and then ALK, that process may take 4 to 5 weeks. Many patients just aren't willing to wait that long to get these results. Advocates for sequential testing have raised the point that KRAS is the most common, so if you check for KRAS and they have a KRAS mutation, you can stop there. Again there's very little, if any, overlap between any of these genotypes. My problem with this approach is that only 25% of patients are going to have a KRAS mutation, so for 75% of patients, all you're going to do is delay EGFR mutation tests. And the same thing would go for ALK; you would just be delaying that. And sometimes that just doesn't sit right with doctors and patients in terms of waiting so long.

So I think in day-to-day practice, the two absolutely clear things you should be testing for are EGFR mutations and ALK

translocations. This is because we have drugs like erlotinib and crizotinib that work better in chemotherapy for these patients who have EGFR mutations or ALK translocations. And if you don't find one of those, I'll go back to my comment about ROS1. I believe crizotinib is probably going to be better than chemotherapy, and that will be very similar to the ALK population. So as a bare minimum in practice, test for EGFR and ALK; if those do not find anything, think about ROS. And beyond that, in day-to-day practice today, I think most other findings would be considered more investigational. Certainly there are other potentially actionable findings that you may find and for which you can get more extensive testing done. One example is that there are a small percentage of NSCLC patients who have either HER2 amplification or HER2 mutations, and we do have some HER2-directed drugs out there that could potentially benefit those patients. We don't have a lot of clinical evidence to date that they're actionable oncogenic drivers, but certainly they would be candidates for targeted therapy if you were to identify those patients specifically.

MODERATOR: Thank you. And again as a reminder to our participants, please press 0-1 if you would like to ask a question. Dr. Geist.

DR. GEIST: Certainly. Dr. Socinski, I have one question for you here from one of our participants regarding the use of targeted EGFR agents in non-mutated patients. What's your perspective on that?

DR. SOCINSKI: I'm sorry, ask me that again.

DR. GEIST: Certainly. They want to know about the use of EGFR-targeted agents in patients who are non-mutated.

DR. SOCINSKI: Yeah, so that's a good question too. I think we've been very impressed in EGFR-mutation–positive patients about the activity of drugs such as erlotinib. We now have at least seven randomized phase 3 trials in the mutant population to show that EGFR TKIs, whether it's gefitinib or erlotinib and coming soon will be afatinib, are better treatment then chemotherapies for those patients. So we know that the EGFR TKIs are really good drugs if you have an EGFR mutation. What if you don't have an EGFR mutation, that's the question, your so-called EGFR wild-type? Well, the data would suggest that in the second- and third-line setting there is a survival advantage for erlotinib versus placebo. When you look at the maintenance trial of

erlotinib, there was a survival advantage in the wild-type population; the impact in the EGFR wild-type population isn't nearly what it is in the mutation-positive patients, but the impact of EGFR TKIs in the wild-type population is not dissimilar to the impact of chemotherapy. So again, if you're willing to use chemotherapy in the wild-type populations, you should be willing to use a drug like erlotinib in the wild-type population. Just remember the impact of that drug is not going to be what you might see in the EGFR-mutation-positive population; it's not going to be too dissimilar from chemotherapy. Remember in a largely wild-type population, we've had several trials that have compared chemotherapy, principally docetaxel to erlotinib or gefitinib. Those trials have suggested that they're largely equivalent in their activity in the population. So I think that one should not discriminate against the use of a drug like erlotinib in an EGFR wild-type population. And I think it's a drug that should be considered for second- or third-line treatment in all patients who have the EGFR wild-type status.

Now we do have information that in a wild-type population in the first-line setting, it is not as good as platinum-based doublets, so I would not use an EGFR TKI in the first-line setting in a wild-type population. However, in the second- and third-line setting, it seems to perform as well as monotherapy that we typically do with cytotoxic agents. So that's my answer.

MODERATOR: Thank you. Dr. Geist.

DR. GEIST: Certainly. Another question that we got from one of our participants asks about your perspective on the sequencing order or the treatment order for patients with advanced squamous NSCLC.

DR. SOCINSKI: Yes. In the squamous patient with advanced stage 4 disease, these patients have fewer options than the nonsquamous population. Bevacizumab is not an option because of the bleeding risk. Pemetrexed doesn't seem to be the most efficacious agent in this setting so most of the time, in the first-line setting, we consider either a carboplatinum with gemcitabine or carboplatinum with one of the taxanes—obviously we have both paclitaxel and docetaxel, but about a month ago, nab-paclitaxel gained an indication in NSCLC. It just so happens that this may be a more active drug in squamous carcinoma than in nonsquamous carcinoma, so I think those are the options for first-line

treatment.

In the second- or a third-line setting I think you have the option of docetaxel or erlotinib. And I talk to patients about what they would prefer, whether they would prefer an IV drug or an oral drug. And with regards to maintenance in this squamous population, I think in general squamous carcinoma patients have fewer options for maintenance so less maintenance is done. In fact, I think the only option they have is erlotinib, really from the SATURN trial, and I will point out that the squamous histology patients did as well as the nonsquamous patients with regard to survival receiving maintenance erlotinib, so it really is an option for those patients. Remember pemetrexed is not an option in the squamous population like it is in the nonsquamous, so they just have fewer options overall, but that's pretty much how I sequence drugs in the squamous subset of patients.

MODERATOR: Thank you. And we have a question at this time, and that question is coming from Kingston, New York. Please go ahead.

MALE VOICE 1: Question one: I presume you would not be doing routine EGFR testing in all squamous cell patients or am I incorrect in that? And number two, in a patient who presents with a neuroendocrine-type tumor, large cell neuroendocrine, do you treat those with etoposide platinum or do you just treat them regularly as a non-small cell?

DR. SOCINSKI: For the first question, squamous is more tightly linked to smoking; however, in my clinic today I saw a patient with squamous histology who quit smoking in 1978 and had a relatively minimal smoking history. So in the squamous population, I do testing if they have a minimal smoking history or perhaps they quit like this gentlemen several decades ago, so we are getting his tissue. In fact he was from your neck of the woods. He actually just moved here from Poughkeepsie, which is close to you, right?

MALE VOICE 1: Yes, it is. Yes, very close.

DR. SOCINSKI: So he moved here because his family was here, and we're going to get his tissue down from, I can't remember the name of the place he was biopsied up there, but there's tissue available to do some testing for EGFR mutations and ALK. They are much less common in squamous carcinoma, but they aren't zero, particularly in squamous patients who don't have much of a smoking history, so I test all

nonsquamous regardless of smoking history but in the squamous, I rely on smoking history to decide whom I'm going to test.

For the second question, in the large cell neuroendocrine I tend to kind of treat them more like I would treat a small cell, and that typically depends upon how fit they are. If they're fit, I tend to use cisplatin/etoposide, but if I think they're going to have excessive issues with cisplatin, I'll use carboplatinum/etoposide.

MALE VOICE 1: Thank you very much.

DR. SOCINSKI: Yeah.

MODERATOR: Thank you. And before we conclude, Dr. Geist, let's provide one final submitted question.

DR. GEIST: Certainly. Dr. Socinski, can you tell our audience a little about the general perspective on the concept of maintenance therapy in stage IV NSCLC.

DR. SOCINSKI: Yeah. So I mean this is my perspective on it. If you look back to around the turn of the century, 1999, 2000, we have the first trial that evaluated docetaxel in the second-line setting, which studied patients who received platinum-based therapy as the initial therapy, completed that therapy, and then at some point following that had evidence that their cancer was getting worse; so they had disease progression, and then they were treated with docetaxel versus best supportive care. There was a survival advantage, and the FDA approved docetaxel as a second-line drug after platinum failure. The next trial we had was the comparison of docetaxel to pemetrexed. They were the same, and then we had BS21 in the same population who had previous platinum exposure, had disease progression, and then were randomized to erlotinib versus a placebo; there was a survival advantage and the FDA approved those drugs as second-line drugs when you were progressing.

So the logical question, well why should we wait for progression? Why don't we treat them right after first-line as maintenance therapy? And then we have this rash of trials exploring the paradigm of giving patients four cycles and then if you didn't have disease progression, you were randomized to get one of the second-line drugs. And both docetaxel and pemetrexed have been tested as maintenance drugs in all of those trials depending upon how

you interpret them. I interpret them as being all positive. But it’s not surprising to me because these are three drugs that if your cancer is getting worse, they’re probably going to work; if your cancer is more controlled and you are fit to receive them earlier, that’s preferable to waiting for disease progression.

The other issue about waiting for disease progression is that all of the studies have shown that about 40% of patients never receive second-line therapy if you wait for progression; therefore, you would deny a patient any exposure to treatment that has a survival advantage if you wait too long, so that’s the concept behind maintenance. To me it’s recognizing that second-line therapy is effective therapy, and the FDA approved these three drugs based upon a survival advantage, so why would we wait for progression? Let’s give them earlier so that more patients can benefit from them. All of the maintenance trials showed that the percentage of patients who received effective therapy was much higher by giving it as maintenance than by waiting for disease progression.

MODERATOR: Thank you. Dr. Socinski. And thank you all for your attention. This concludes today’s Advanced Non-Small Cell Lung Cancer Community of Practice Audioconference, which has been sponsored by Med-IQ and supported by an educational grant from Lilly USA, LLC. This activity is part of the complementary PI CME series, Performance Improvement Strategies in Advanced Non-Small Cell Lung Cancer. To learn more about this complementary CME series or to enroll today, please visit www.pi-iq.com/NSCLC. Thank you for your time and commitment to improving the care of patients with lung cancer.