A Lung Cancer Roundtable: Takeaways From ASCO 2018

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Andrew Schorr:
Hello and welcome to this Patient Empowerment Network program produced by Patient Power. I'm Andrew Schorr from Patient Power, and we're discussing an update from the big American Society of Clinical Oncology meeting, ASCO, and what it means for patients and family members dealing with lung cancer today. I want to thank our financial supporters for making grants to support this program, Celgene and Pfizer.

So we have two noted experts with us. We have Dr. Jeffrey Crawford from Duke University and the Duke Cancer Institute in Durham, North Carolina, and Dr. Edward Kim from the Levine Cancer Institute down the road also in North Carolina, in Charlotte, North Carolina. Dr. Crawford, welcome to Patient Power and the Patient Empowerment Network.

Dr. Crawford:
Andrew, thank you. I'm glad to be here.

Andrew Schorr:
Dr. Kim, welcome to you.

Dr. Kim:
Pleasure, Andrew.

Andrew Schorr:
Okay. Gentlemen, let's start. So I walked into the ASCO exhibit hall, which is many football fields wide and long, and I was impressed with so many companies devoted to helping doctors and their patients understand the specific biology, molecular composition of the tumor that somebody might have, for example, with lung cancer. Dr. Kim, is this where it's going, is that sort of precision medicine? And why is it so critical for patients and their doctors?

Dr. Kim:
Yeah, thanks, Andrew. I think it's really important to know how the new standards are changing. We've been used to a lot of therapies and how we assess folks for decease such as biopsies and histological diagnoses, and now it's not just about that. It's about trying to figure out what genes exist that are unique to each person's individual tumor. And we know that these genes are differently made up in different folks, so just to call somebody who has a non-small cell lung cancer, and that's the area that myself and Dr. Crawford cover, is really not the whole picture anymore.

We've seen this in breast cancer. We've just kind of come to accept it over the last couple decades, that you're either a hormone receptor-positive breast cancer patient, or your tumor is HER2 positive or not or you're a triple negative, and that's means none of those markers are present.

Well, we were never that sophisticated in lung cancer, frankly, to have the equivalent of a triple negative even though we did, and we started is seeing this in the early 2000s, especially as we looked at first the mutations like EGFR and translocations like ALK and ROS1, and now that number is just really exploding as far as the number of markers that a clinician has to check just at baseline to make the proper assessment to treat a patient with non-small cell lung cancer these days.

And that's exciting, but it's also daunting in that the data and the drugs and markers are changing so frequently that it's hard to keep up, and even as an expert it's hard.

Andrew Schorr:
Now, Dr. Crawford, you're in research a lot as well, and so this multiplying of genes, you keep identifying new ones, right, and then it's a matter of finding out, well, which genes are important at which time for which patient, right?

Dr. Crawford:
Correct. As Ed was saying, it's a complicated task, and I think we get now a lot of information. When we do next-generation sequencing, we get literally hundreds of genes. Some of them are actionable, some aren't, and really understanding which are and which aren't and how to interpret that is becoming a field of its own. So molecular tumor boards have started to try to dissect this at the institutional level so people can sit down with pathologists, like the pathologist-clinicians, try to work through how to move forward on an individual patient basis.

Andrew Schorr:
So, Dr. Kim, we hear about immuno-oncology, immunotherapy, and drugs that are being tested in many cancers to try to help the immune system be boosted, I guess, to fight the cancer. Maybe you could explain that because there was news about that at ASCO, wasn't there, for lung cancer?

Dr. Kim:
Yeah. And certainly it seems like every major meeting, Andrew, has news about immunotherapy. And the really nice part about it, speaking very selfishly, is that there has been a lot of news about immunotherapy and lung cancer, and I get to tease my melanoma colleagues, that, yeah, you know, we know it's been around for greater than five, six years in melanoma. But it required a large scale sort of cancer to take this into the main stream.

And lung cancer is one of the largest. It affects so many people out there, and to have these trials testing immunotherapies and these FDA indications, has really transformed things. What we explain to people is that it's not like the vaccine programs in the past in that the immune system is a very sort of gray area for a lot of folks. Some people think you can take vitamins and boost your immune system. Other people think you just have healthy living it

will do it, and all those things contribute, because your immune system is really like your micro environment throughout your entire body, and a lot of things affect it, and it affects a lot of things.

But what's really cool about these newer generation drugs that are impacting the cancer process is that cancers have become smart. They are able to build up defenses to be sort of stealth inside the body, and so even though there were bad things happening to you your body couldn't tell that they were cancer cells versus normal cells. And so these new checkpoint inhibitors have focused on trying to break down the stealth or the defenses that these cancer cells have been using to invade the immune system.

And so now you're really empowering your own body's immune system to fight the cancer. And that's really exciting. The side effects, there are some but have generally been very well tolerable. There are always a percentage of patients who can get a hyperactive immune system, and that's usually what causes a lot of symptoms we see. But all in all—you know, we use Jimmy Carter as a poster child, he's like 150 years old, and he's on an immunotherapy being treated for a stage IV melanoma and doing very well. So that's what my patients see out there, that's why they're asking about it. We have to select the right people who is appropriate.

Andrew Schorr:
Well, Dr. Crawford, let's talk about selection. So we've alluded to testing to understand what's at work or what sort of immune levels, we hear these terms PD-1 and PD-L1, and they're even mentioned on telephone commercials for lung cancer drugs. So how do we know whether this changing world of immunotherapy applies to an individual patient?

Dr. Crawford:
Well, that's a good question. So I think we're learning as we go about biomarkers for immunotherapy, but certainly the one that's out there most notably is PD-L1, and so that's a marker of this protein that Dr. Kim was talking about. It's an immune checkpoint, so PD-L1 when it finds the PD-1 receptor down-regulates or lowers the immune system, and that's a natural, naturally occurring process. It's important so our immune system does get overly revved up, but what happens in cancers it often gets overly depressed and suppressed, so we have inhibitors, drugs that work by inhibiting that reaction that allow the immune system to emerge and attack the cancer.

So what's really cool about this is that the immune system itself is what destroys the cancer when you take these agents. This is not like chemotherapy or even targeted therapy where there's a direct cytotoxic effect on the cells. This is really enabling your immune system to take over and attack the cancer and destroy it. So it's remarkable when we see an X-ray with cancer disappearing based on restoring the immune system.

So PD-L1 is clearly an important marker, because it's the way these first-generation immune checkpoint inhibitors work through that process. So one would assume that the PD-L1 measurement would be predictive of who is going to benefit and who is not. And in some sense it is, but it's not at all like EGFR testing, where we are pretty confident when we have an EGFR mutation we'll have a very high response rate, while with PD-L1 even in patients with expression above 50 percent only about half of them get a good response.

And on the other end patients with very low response, very low levels of PD-L1, they still have a response of 8 or 10 percent. So it's not a perfect marker by any means, but it has been helpful in identifying patients likely to benefit. And what's come out of ASCO is more and more about how to select patients for immunotherapy or a combination of chemo and immunotherapy or other options.

Andrew Schorr:
Dr. Kim, let's talk about biopsy for a minute or how you get the information from the patient as to what's going on

and then what to do about it, if you will. So getting a lung biopsy is not easy, and I know sometimes there's a problem getting enough tissue to do all the analysis you want, and now we've been hearing about more and more companies that are doing liquid biopsy. Okay.

So here's Mr. Jones, you want him to have a lung biopsy. Would there also be a liquid biopsy or l—and not just at diagnosis, but would you be doing some of this along the way to see if treatment is working?

Dr. Kim:
Yeah, we've always been attracted to some of the other cancers that utilize liquid tests, ovarian cancer, CA125, PSA, prostate cancer, although we're still not really clear on where we're supposed to be using that to screen patients, but that has given people is principle that they like to follow things. And that's why cholesterol, for instance, was such a powerful sort of marker even though the relevance of it has been questioned by cardiologists. People can see there is an effect.

So, first of all, we have to say that nothing has completely replaced tissue. That is really the gold standard. It still is. I tell our interventionalists, whether it's a pulmonologist, interventional radiologist or anyone, I don't want a diagnosis. I want tissue. Because they can make a diagnosis by doing some brushings or some cytology, and they can tell me it's an adenocarcinoma favoring lung. That is not helpful. We need to absolutely have data that allows us to send for these molecular tests, which includes, as Jeff mentioned, PD-L1.

We need EGFR mutation, ALK, ROS1, BRAF. These are all very important markers now that need to be sent. And in some cases, at some centers they send for the larger panels. What you get are 3- to 500 genes. I don't need 3- to 500 genes, but there are certainly clinical trials out there that can help match patients into trials based on these genes, so it is some utility.

But the blood-based markers and the biopsies are improving. There are definitely very—there are good data that show concordance when they're positive. So if you do a blood test and it shows a positive mutation for EGFR, for instance, you can be pretty confident that the tissue has that as well. The problem is that when you get a negative result. And the negative result, those percentages aren't disconcordant, because they really show the amount of accuracy, and so you can't take a negative test at face value. We don't standardly do liquid biopsies in patients unless the patient really has a contraindication to doing a traditional tissue biopsy.

As far as the surveillance aspect, as you mentioned, we do that on research. So on our research studies we do follow patients at every cycle with another blood draw, in addition to what they give in labs, so it's not an extra stick. It's just extra biopsy. And we do try to follow to see if we can see some of these different mutations either go up or down based on how the treatment is working or not working. And we're hopeful that this type of research down the road can lead to more predictive assays that are easier to gather, so we can either surveil patients to see if they have cancer, if it's gone away, if it's come back.

You can imagine somebody who has been treated for cancer, who has no evidence of disease on a CAT scan but maybe with blood surveillance we can get an early sign if something is coming back. These are all possibilities and are being investigated, but right now it's really a backup plan if tissue can't be adequately gathered.

Andrew Schorr:
Dr. Crawford, of course, you're doing research as well. Do you agree with this, where we are now and where we're headed?

Dr. Crawford:
Absolutely. I think what's happened in lung cancer is because of this need for tumor tissue, as Dr. Kim has pointed out, it's really transformed all the interventional things we've been doing. We were moving in the '90s to smaller and smaller biopsies, smaller and smaller needle aspirations just to make a diagnosis, but now we've gone back the other way where we're retraining our pulmonologists to get larger cores of tissues. They're developing new techniques to get more tissue, endobronchial biopsies. CT interventional people have been enormously helpful for getting core biopsies, so we get adequate tumor tissue to do the molecular tests we've been talking about.

So that's really fundamentally important and important to have at every institution hospital across the country. It's one thing for Levine or Duke to be able to do this, but it really needs to be done in smaller community hospitals and done well by interventional people who can get the tissue we need, because the samples can always be tested at a central site if the pathology labs can't do it locally. We have to be able to get the tumor tissue.

Andrew Schorr:
Let's pull this together for a little bit. I want to see if I've got this right. So you're having a revolution now in more genes being identified and trying to decide what's actionable, whether you have approved medicines or combinations or drugs in trials, that both of you have alluded to, could for research purposes you identify something and where that could offer hope to a patient where otherwise the existing therapies might not match up?

So what actions should patients and family members be talking about? And you said, Dr. Crawford, like at the community level or if they have a university hospital as a choice to go. What should they be doing now? Because obviously anybody diagnosed with lung cancer or their family member, we want the longest life and the best chance right now, and yet you have an evolving field. So what would—Dr. Crawford, how would you counsel patients and family members so that with what you have available, either as approved therapies or in trials, could be available to them?

Dr. Crawford:
Well with, first, let me back up a second to say we've been talking mainly about advanced lung cancer.

Andrew Schorr:
Right.

Dr. Crawford:
So it's important that patients get diagnosed early. It's important that patients who are eligible for CT screening and to go that, so we can detect lung cancer at an earlier stage and hopefully offer them curable surgery. And then for them to get evaluated by a multidisciplinary team if they're in early stages to see is surgery alone the right thing, surgery and chemotherapy, a combination with radiation, so all those standards are still present in early-stage disease.

Now, as we may talk about, immunotherapy and targeted therapy may have a role there as well, but I think our curative strategies remain intact there. So it's very important to have availability of a multidisciplinary team that can really assess cancer at all stages.

For the advanced cancer patients then, what's particularly important is for every patient to get molecularly defined tumor testing being done. So we not only need to know the pathology, as Dr. Kim has said. We really need to know the molecular phenotype of cancer to really make the best treatment approach for patients with advanced disease. And in most patients, that should happen before they ever talk about chemotherapy. We need to know are there better approaches for that patient, and we're not going to know that without these tests being done.

Andrew Schorr:
How about you, Dr. Kim? I mean, still chemotherapy is still around, still in combination. People understand there are side effects, not that there are not side effects with the new immunotherapies, but people would like to skip to the most effective treatment first. So what recommendations would you have for our listeners?

Dr. Kim:
Yeah. You know, we're talking strictly about the advanced lung cancer patients. The new standards in non-small cell, both nonsquamous and squamous, now contain an immunotherapy combined with chemotherapy in markers that are lower selected or unselected. I agree with Jeff. You know, the biggest struggle we always want to tell our patients is be patient. Do not let the chemotherapy start without having the results of your markers.

And that's where sort of this new diagnosis of cancer comes in, the fear of it growing while you're waiting a couple of weeks for the results of these markers, but we have to reassure patients it's okay because if you just wait the extra one to two weeks.

And I understand it could take longer getting the biopsy to get enough tissue, sending it away, taking three weeks, and then your doctor, who is maybe not as sophisticated at reading these very, very, 18-page reports, take some time to evaluate it. It could be five weeks right there very easily, and we don't like to wait that long.

But if you do have a marker present, and if it is—and now almost 50 percent of the patients with non-small cell have this, have a marker, maybe we'll be able to give you something in lieu of chemotherapy that's not a pill, single-agent immunotherapy. And certainly as a default now we're seeing again new standards of care. New standards of care are combination therapy, chemotherapy with immunotherapy based on data that's been presented in the last couple months.

And so as a biomarker person I love seeing marker-enriched populations receiving less therapy, but as we begin to incorporate these drugs in our standard regimens we're seeing improvements that are undeniable and are forcing us now to readjust or new standards.

Andrew Schorr:
Dr. Crawford, so I've heard along the way, and I know knowledge is expanding, whether or not some of these newer approaches apply to people whether—you know, whether they smoked or not, whether they had a history. Where are we now with having the widest array of approaches for the widest array of people whether they're smokers or not?

Dr. Kim:
So smoking is clearly an important factor in outcome for patients, and it's also somewhat predictive of likelihood of different things. We know smokers have a lower rate of EGFR and ALK translocations, mutations. We also know that they have a higher rate of PD-L1 expression and may be more likely to respond to some of these immunotherapies, but those are just generalized statistics. And we have smokers who have EGFR mutations, and we have never smokers who respond beautifully to immune checkpoint therapy, so the answer is we have to do the molecular testing and sort out who has what. Smoking may influence that frequency, but on any individual patient basis we have to have the tests to know how to best to treat them.

Andrew Schorr:
That's good news. So, Dr. Kim, you had referred earlier about cancer being kind of wily, if you will. So is it possible that the molecular testing results at time of diagnosis further down the road may be different? In other words, some

other gene is driving the cancer should it come back or it's still going, and you need a different approach. In other words, you have to change horses, if you will.

Dr. Kim:
Yeah, that's a great point, Andrew. You know, back in 10 years ago, almost 11 years ago when we initiated this trial while I was at MD Anderson called BATTLE, the whole principle was to re-biopsy patients once they completed or once the first line of therapy stopped working. And for that very point you brought up is that these tumors change. If you use a baseline tissue, that's a very different environment that that tissue was exposed to. It has not been treated with chemotherapy, it's not been under different stressors, and nor has it now begun growing after getting chemotherapy.

So a patient, just as you say, who has been treated maybe there was some success but then it—with chemotherapy it's always a little transient, and then now the tumor is growing despite being treated, that could be a different tumor. It's been shown also by the Boston group that you get transformation to small cell, of all things, in about 15 percent of patients. And so different histologists altogether. So who knows what will evolve out of the cancer that's been treated that is now beginning to grow.

And so I think it's really important to have a repeat biopsy when this occurs to help again drive the appropriate treatment. And, as we talked about earlier, if it's difficult sometimes a liquid biopsy can even be done at this setting if it's difficult or the patient is has a difficult area to get tissue.

Andrew Schorr:
So, Dr. Crawford, you have lung cancer meetings throughout the year, but the ASCO meeting with like 40,000 people across all cancers from around the world, it's a big meeting. You're involved in research and, of course, with existing therapies as well, how positive do you feel about change and even the rate of change to offer hope for people dealing with lung cancer today?

Dr. Crawford:
I'm as excited about lung cancer as I've ever been, and I've been doing this for quite a while. The rate of change is, as Ed has pointed out, is dramatic. The number of new agents that we have seen over the last year, both targeted therapies and immunotherapies, and the rate of change, it's not just ASCO every year. AACR, a meeting that's normally more basic research, had major breakthrough discoveries as well I'm sure this year, and Europe will have additional new discoveries as they did last year.

So it's really changing every few months, our guidelines through NCCN have to be changed almost monthly, and I think that's a good thing. It's telling us that new knowledge is really being moved very quickly into the patient care arena.

Andrew Schorr:
Dr. Kim, so we've talked largely about non small-cell lung cancer, and you've rattled off some of the different types. There's a percentage of people, smaller percentage, but people with small cell-lung cancer. Were there things you were hearing there at ASCO that could offer hope or in research to help this population as well?

Dr. Kim:
And certainly Jeff is the expert here. He's had a long career with it. Small cell has always been that tough cancer where you get teased a little bit. Again, if you're fortunate enough to find someone in limited stage, you can try to deliver curative intent therapy. If they happen to be in an extensive stage, it really becomes about trying to give chemotherapy that has a high response rate, and so you feel good about that, but then the difficult aspect of it is that

in fact it doesn't last forever. And so when it does again not respond, it's not responding, we've got to figure out some things.

The immunotherapies have been very widely tested, and so there are some therapies that are coming. There are some that are approved, nivolumab (Opdivo), ipilimumab (Yervoy) have been used. They're trying to incorporate in combination with chemotherapy with these immunotherapies. There are some other drug classes, Rova-T (Rovalpituzumab Tesirine) and others that are being looked at very closely in small cell. So I love the fact that there's spillover in the small cell, because it wasn't really a high area of importance for a lot of development of drugs, which was unfortunate because we still see those patients, but it's nice to see that there's a lot of studies been looking at these types of drugs.

Andrew Schorr:
Okay. Dr. Crawford, any other comment you wanted to make about small cell?

Dr. Crawford:
I would say it's an area that's been difficult to see advances. Small cell presents generally at more advanced stage, so very few patients can have surgery. Chemo and radiation can still be curative for early-stage patients with lymph node involvement who don't have distant disease, but in the advanced stage setting we've been using the same chemotherapy for 20 years. Our supportive care has gotten better, we've made some advances, but we're hoping immune therapy and others will make a difference.

It's kind of interesting. Small cell, you would think, since it's prevalent largely in smokers, people with smoking exposure, could be very—a lot of mutations being present. We know that total mutation burden is a nice predictor of benefit in non small-cell lung cancer, so we think that would—might play out here. There is PD-L1 expression in small cell but it's not as intense. And there is some separation by PD-L1 score of benefit for immune checkpoint therapy in small cell, but the responses in general are less than they have been in non-small cell. So we're going to need more, more homework to figure this one out, but I think we're taking some steps in the right direction.

And as Dr. Kim pointed out, Rova-T is a targeted therapy, maybe one of the first targeted therapies we've had in small cell that attacks antigen present on a lot of small cell called BLL3, and there are other therapies being developed against that BLL3, because we know that's an important marker. So I hope we will see agents that are truly targeted therapies in small cell in the next few years.

Andrew Schorr:
Okay. So I think as we pull this together, and I think you were rattling off some acronyms, and that's sort of what we've been seeing a lot in lung cancer now. We've talked about EGFR and ALK and ROS1, and we talked about also PD-L1. So I know for patients it can be confusing, but look back, review this program with Dr. Crawford and Dr. Kim were saying about if you have someone diagnosed with advanced lung cancer to get that molecular test and get that more complete biopsy to make sure that the experts like this and your local doctor if you're not treated in a university or in your major center like this, that they have the information. And then if you need to get a second opinion, Dr. Kim, you said it's an 18-page report you may get back. So obviously the community oncologist has a lot to sort through, but there's help in second opinions from people like this. Dr. Crawford, did I get it right?

Dr. Crawford:
I think you did. You're a good student.

Andrew Schorr:
Okay. All right. Well, we have two professors with us, Dr. Edward Kim from the Levine Cancer Institute in Charlotte,

North Carolina, my old home town, and Dr. Jeffrey Crawford from Durham and Duke University. I'll say that even though I went to the University of North Carolina eight miles down the road.

Dr. Kim:
You had to say that.

Andrew Schorr:
Yeah. Thank you. Thank you both for your work in treating patients and in researching, helping give us a window into this ASCO conference, but I get the sense you—you said it, Dr. Crawford—you're having meetings every couple of months and talking to your peers all the time, and this is a faster changing field. Thank God, right? So thank you so much. Dr. Crawford from Duke, thank you so much for being with us.

Dr. Crawford:
Andrew, thank you so much and thanks to all the patients who are joining in today. It's for you we do all that.

Andrew Schorr:
Yeah, thank you. And Dr. Kim, thanks. I interviewed you years ago, and you were at MD Anderson. Now you're in Charlotte, and you have a wonderful program there. Thank you for being with us.

Dr. Kim:
Thank you, Andrew. It's our pleasure, and again, we're just as excited as the patients, because we get to offer them these really cool therapies and research studies.

Andrew Schorr:
Right. Okay. All right. All the best to our patients and family members watching. For the Patient Empowerment Network, I'm Andrew Schorr from Patient Power. Remember, knowledge can be the best medicine of all.