ASCO 2017 Roundtable: Progress in Lung Cancer on Multiple Fronts

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Andrew Schorr:
Hello. I'm Andrew Schorr, and this program is a Patient Empowerment Network program produced by Patient Power, and we want to thank Pfizer, Genentech and Celgene for their support.

And we're, of course, talking about lung cancer. We're sort of at one of the major meetings of the whole year, and that is at the American Society of Clinical Oncology meeting in Chicago, the ASCO meeting. Now, there are lung cancer meetings around the world, and they happen throughout the year. So this is more in the momentum of what does research mean for doctors, what does it mean for patients, families affected by lung cancer.

And I'm really happy to tell you we're joined by two leading clinicians in the field, researchers in the field, who are plugged into action central in what's going on in lung cancer and what it means for you and your family.

So joining us is Dr. David Carbone. Welcome back to one of our programs. And, of course, you are the Director of the lung cancer program really at the James Cancer Center at Ohio State University in Columbus.

Dr. Carbone:
Yes.

Andrew Schorr:
So thank you so much for being with us.

Dr. Carbone:
Thanks for having me.

Andrew Schorr:
And also Dr. George Simon who joins us from MD Anderson in Houston. You're a Professor in Thoracic Oncology and Head and Neck Cancer as well there. Thank you for being with us.

Dr. Simon:
Thank you for having me.

Andrew Schorr:
Okay. Let's start with you, David. So what's the buzz here that would be meaningful in the sort of drumbeat of progress for people living with lung cancer?

Dr. Carbone:
Well, the buzz for lung cancer is continuing progress in virtually every front of managing the disease. We have new data being presented on new drugs that are more effective at getting into the brain and preventing and treating brain metastases. They produce longer remissions. They have better quality of life for patients. We have new types of immunotherapy and new indications for immunotherapy being presented, and the progress is across the board and very exciting.

Andrew Schorr:
What's your view, George?

Dr. Simon:
I agree with that entirely. I think we are making progress in multiple fronts in targeted therapies. We're getting better drugs, more effective drugs. In immunotherapies, we are getting a better understanding of how best to use them, in what setting, more data on some of the rarer thoracic malignancies and the role of immunotherapy in those, novel immunotherapy combinations. So, yes, I agree with David. We are having progress, fairly relentless progress on multiple fronts.

Andrew Schorr:
Okay. We're talking about terrifying diagnosis, David. Someone's diagnosed yesterday, and they—some family member is watching TV today, and now they see TV ads for some of the drugs in lung cancer. And they say, does that apply to me or my loved one, because it seems hopeful? So how do we know what's right for what patient?

Dr. Carbone:
So it's very clear that we have a lot of new therapies, and they're active in some patients and not other patients. And I think the first message that needs to be made very clear is that the cancers need to be characterized for a variety of markers before any treatment gets started, because everyone's cancer is different from everyone else's cancer. And we have much better knowledge today about specific features of cancer that are associated with benefit from one drug versus another.

And so in spite of the television ads, those drugs are not appropriate for some patients, and they're exactly the right answer for others. And patients need to have a conversation with their physician where they demand that their tumor have genetic analysis, immune biomarker analysis for PD-L1, and all of that information needs to be available to choose the best therapy for that patient.

Andrew Schorr:
Now, you are at the James Cancer Center in Ohio, Columbus, Ohio. You're working in your own state, in Ohio, to make that a realty throughout the state that people get tested, right?

Dr. Carbone:
Well, in spite of the state-of-the-art saying that we need to know the molecular features of cancers before picking therapy, the sad fact is that many patients have therapies chosen at random, don't have the appropriate molecular analysis, and not all of the actionable things, not all of the really useful markers that we have today are even part of many hospitals' panels.

So what we're doing in the state of Ohio is we're trying to capture every new advanced lung cancer patient in the state, and we're providing free, up-front advanced genomic testing as well as PD-L1 immunologic marker testing to those patients. And we're trying to show that that testing provided at the time of diagnosis improves the survival of these patients.

And I think not only can we use that information to convince payers and healthcare systems that this is important, but I also view it as an education for community physicians who may not have PhDs in genetics, like I do.

Andrew Schorr:
So, George, let's talk about this. So sometimes I view cancer, and lung cancer is a good example, as almost an alphabet soup. You have these different letters, ALK and ROS and EGFR, and applying to, as I understand it, genes, cancer genes that are doing bad things, sometimes more than one even, right? And this is baffling to patients until they begin to learn.

So could you help us understand where therapy is headed to try to turn off some of these genes, targeted therapies? And then we'll talk about how immunotherapy works. So, first, targeted therapies, so if somebody has an ALK gene, which some lung cancer—what does that mean if you have a medicine that fires at that?

Dr. Simon:
So a simple way of thinking about lung cancer or a good way of thinking about lung cancer is to think about it as a few cells gone awry. So in natural cellular metabolism and cell division the rate at which the cells die and the cells are regenerated are about same, and so there is a uniform balance.

Andrew Schorr:
An equilibrium.

Dr. Simon:
An equilibrium. Now, sometimes what happens is a mutation occurs in a critical area which upsets that balance, that tilts the balance in favor of uncontrolled growth, and growth happens in an uncontrolled fashion, and spread happens, and there is no check to that. So cancer is nothing but a few cells that are now growing uncontrollably.

In a way, you can think about this mutation as a switch that has got turned on and then is never turned off. So what these targeted therapies do is turn the switch off. And by that you're able to then control the growth rate, and actually many of the cells will wind up dying, and that equilibrium to a certain extent is restored.

Now, these drugs are very mutation specific. So if you have an EGFR mutation, you have to have a drug that shuts down the EGFR mutation.

Andrew Schorr:
And you have some now.

Dr. Simon:
And we have, and we do the same thing for ALK. So in terms of understanding this, a good analogy is vitamin deficiency. So if you have vitamin C deficiency and I give you vitamin D, it's not going to help you. But if I give you vitamin C—if you have a vitamin C deficiency, I give you vitamin C, this fixes the problem.

Andrew Schorr:
Okay.

Dr. Simon:
So that is why it's so critical for us to understand the molecular underpinnings that are driving a specific patient's cancer. Once we understand that, then we can give you the specific drug that will shut down or turn the switch off, so to speak, and induce a high percentage and fairly long-term remissions in these patients.

Andrew Schorr:
Okay. Let me go to you, David, about immunotherapy. So my understanding is when we start making these bad copies, cells gone awry as you said, our immune system has let us down. It didn't identify that. So is the whole idea of some of these immunotherapies to try to correct that, identify those cells? And also add to your answer if you could, can it work with some of these targeted therapies? Can it do both?

Dr. Carbone:
So I wouldn't say the immune system has let us down. It's more that the cancer has figured out a way…

Andrew Schorr:
To outsmart the immune system.

Dr. Carbone:
…to outsmart or to disguise itself from the immune system. And one of the major ways that the cancers use to disguise themselves from immune recognition is to overexpress this protein called PD-L1, which acts like a force field around the cancer, and the T cells can come and try to kill—the immune cells will try to kill the cancer, and they get switched off by this PD-L1 protein expression in the cancer. And we have we now have drugs that block that protein specifically and can reactivate the immune system to recognize the cancer.

Now, like any therapy in oncology, this is not—does apply to every patient, and the patients with these driver mutations like EGFR tend to avoid the immune system by different mechanisms, and those tumors tend not to be as good of targets for immunotherapies. But we're just learning how to best identify patients who benefit or won't benefit from immunotherapies, but it's pretty clear that patients with EGFR-mutant tumors tend not to do as well with immunotherapies as some other groups of patients.

Andrew Schorr:
Okay. While you're talking about that, I just want to quiz you. There are some other mutations I hear about, like ALK or even ROS1. What about in that case? Does immunotherapy play?

Dr. Carbone:
Well, we're still learning, and we're studying exactly that. Many of the large immunotherapy trials, the ones you see on television, excluded those patients, because there was early data that they don't respond as well. And so I think it's not exactly optimal for those patients to receive immunotherapies up front. And if you have an EGFR mutation, the first treatment should be a targeted therapy against EGFR, not immunotherapy, in my opinion.

But we really don't know, for example, for some of the less common mutations like BRAF mutations, that's a very clear driver, but I have patients with BRAF mutations who do well on the targeted therapy and then do well on immunotherapy. So we're just learning which patients to use what treatments for.

Andrew Schorr:
Okay. So, George, let's get to kind of the flow of news a little bit. I know even here at this meeting some hasn't come out yet, you've had other lung cancer meetings leading up to this, so these are the questions you're trying to answer. For patients living with lung cancer today, then where is the news headed that can give them hope, these questions you're trying to answer, that could make a difference in the near term?

Dr. Simon:
So in the near term I think we'll see some exciting data come out in the next day or so. More recently, we have now seen data with the combination of chemotherapy and pembrolizumab (Keytruda) showing very good efficacy in terms of…

Andrew Schorr:
One of these immunotherapies.

Dr. Simon:
…one of these immunotherapies, and in a subset of patients when they combined chemotherapy and immunotherapy the results were very promising. And so that is one of the recent developments that is exciting.

We also have learned from a recent publication just about a week or two ago where sometimes you may be able to augment the efficacy of pembrolizumab, one of these immunotherapies, by giving them some radiation first. In retrospective analysis they found that patients who got radiation for some reason, for, say, a painful area or to the brain, and then got pembrolizumab they seemed to get more effect out of it.

So these are things that we are trying to understand as how sometimes we can use the various tools in the shed that can be optimally combined to get optimal results.

Andrew Schorr:
So combination of medicines but combination of modalities as well.

Dr. Simon:
Yes.

Dr. Carbone:
Radiation and surgery. There are studies that are looking at immunotherapy in patients who have resectable tumors as well.

Andrew Schorr:
Okay. So what news has been developing from studies, David, even maybe some that's been seen overseas that gives us a window into what may be a big deal here?

Dr. Carbone:
Lung cancer is a global problem, and there was a very exciting study from Japan called J-ALEX that showed that using one of the newer generation drugs targeting THE ALK mutation positive tumors, using that new generation drug first produced an incredibly long duration of benefit for those patients, and in fact seemed to prevent the development of brain metastases, which is very common in that population and is a huge factor in the quality of life that these patients have.

And in fact the newer drug also has less side effects. So the newer drug when used first seemed to be better tolerated, have a better quality of life for patients where the benefit lasts for longer, and prevents the development or delays of development of brain metastases in these patients. So it's a very exciting result and may lead—and actually has led to first-line approval in Japan, and we're hopeful that that will happen soon in the United States.

Andrew Schorr:
Okay. So you have some publications coming out. Can you give us a window into any of the hot stuff you think, at least the significance for patients?

Dr. Carbone:
So we are looking for ways to better tailor treatments to patients, and one of the ways for immunotherapy is looking at using it in patients that have high levels of the PD-L1 protein. But even with high levels of the PD-L1 protein, half or less of patients get major shrinkage of their cancer.

We've recently done a study that showed that if you look at another parameter of the tumor, which is called tumor mutation burden, is independently predictive of benefit from immunotherapy. And so patients who had both the high PD-L1 and a high mutation burden, which is assessed by sequencing the DNA of tumors, had a much higher response rate. Seventy-five percent of those patients responded to the immunotherapy, compared to the same patients in the chemo arm. Only 25 percent of those patients responded to chemotherapy.

Andrew Schorr:
So, George, what I hear out of this is you're developing ways to see what approach will work for which patient through a genomic analysis, etc.

Dr. Simon:
That's exactly right. So by looking at these various parameters, mutation burden, PD-L1, specific mutations, we will now be able to specifically tailor a treatment regimen or a treatment strategy for an individual patient. And David talked about immunotherapy not working very well for EGFR and ALK, but one exception to that rule is another mutation called KRAS.

Now, KRAS is commonly seen in patients with—are heavy smokers, and some of those patients may actually respond to immunotherapy, particularly if they have another mutation called p53. Whereas if KRAS is associated with a mutation called SDK-11, then they do not respond. So that is why it's now critical to sort of really understand at the very detailed level what the specific mutation profile is, and then we can tailor treatment accordingly.

Andrew Schorr:
Okay. Testing, testing, testing. And one question I want to ask you, David, is cancer mutates. So we talk about mutations at a certain point, but it can change again. So thank god there are people living longer with lung cancer, but their lung cancer can change, right, either because of the therapy or because of the course of their disease, right, so they may need to be tested again?

Dr. Carbone:
Right. So cancers in order to develop at all have to have evaded all of the normal checks and balances in a patient, and therefore they have evolved to have specific mutations that allow that. When you treat them with targeted therapies they continue to evolve, and we now know in several situations that they can acquire new mutations that make them resistant to the first drugs that we have used with success, and the patient's tumor then becomes resistant.

But we now have second-, third-generation drugs that we can tailor to these new resistant mutations and get durable second responses. And so in many cases now in lung cancer oncology we not only do the genetic molecular testing on the original sample, but we have to resample the tumor when it starts to grow again to look for new mutations and new ways we can target the tumor.

Andrew Schorr:
Right. And I know there's an issue sometimes in getting a new biopsy sample, and now we have liquid biopsies that may come into play as well, right?

Dr. Carbone:
So there are technologies for detecting these gene alterations in the blood, and these tests aren't perfect, no test is perfect, but they can in some situations allow us to tailor therapy without doing a biopsy and just by analyzing a blood sample.

Andrew Schorr:
So, George, we've talked about progress in non-small cell lung cancer. We've heard a lot about that medicine. Small-cell lung cancer, which I know is the minority but still people get so sick, where are we with that, with progress for that?

Dr. Simon:
So we are starting to make some progress there too. For the last 40 years the chemotherapy for small cell essentially hasn't changed. It consists of a platinum and a drug called etoposide (Toposar), and it's not for the lack of trying. For the last several decades, we have had many randomized studies looking at newer drugs, vaccines, all of which have come back negative.

But more recently we have identified a marker called DLL3 against which we have an antibody drug conjugate, an antibody that binds to this marker, and a chemotherapy drug is attached to the antibody which then links to this marker. And a drug recently in a smaller Phase II study is showing promise with response rates of about 25 percent.

We've also gotten better, gotten a new drug called G1T28. G1T28 is a CDK 4/6 inhibitor. What it does is it—one of the side effects of chemotherapy is it causes your blood counts to go down, your white cells and red cells, and so it limits our ability to give chemotherapy in the doses that we want to give. However, because of low counts sometimes we have to delay chemotherapy, sometimes we have to drop down the doses, and that could potentially affect its efficacy.

But this drug actually puts the hematopoietic cells, the blood bone marrow cells, into sort of a state of sleep, what we call G-1 arrest. And when we come in with our chemotherapy then these cells, hematopoietic cells, are essentially resistant to the chemotherapy. So therefore we may not see the level of low counts, or myelosuppression, with those drugs. So that may be a promising approach which is showing some promise in early studies in this ASCO.

Another approach that's showing some promise which needs to be validated is a PARP inhibitor. One of the ways tumors become resistant to our chemotherapy is that it repairs the damage done by the chemotherapy, ability to repair the DNA damage, and many of the drugs we give kills cancer by causing DNA damage. So if we are able to inhibit their ability to repair the damage, then we may enhance cell kill.

So these are some of the newer in my opinion more exciting approaches that are showing promise, although we'll have to validate this larger randomized trials.

Dr. Carbone:
There are also early signals that immunotherapies will work in small cell.

Andrew Schorr:
Right.

Dr. Simon:
Right.

Dr. Carbone:
In fact, there are very good response rates in early phase studies with that disease as well.

Andrew Schorr:
For the people watching and what you know is happening here and what you've been doing in the lab and in the clinic and at the meetings you go to, do you want to give people a message not just of hope but that there are actions to be taken to help them get the right care and do better?

Dr. Carbone:
Patients are their best, their own best advocates. They should be out there aware of the general things that are available and insist that their physician do the appropriate molecular testing to choose the right treatments. And that gives immediate hope that they may have the appropriate treatment delivered. But also I think the other thing that should be emphasized is that progress is continuing at a very rapid rate, and even though something isn't available today by the time they need the next treatment there may be a totally new drug or treatment approach available. So patients should—should be hopeful that they can enjoy good quality of life for longer than ever before and look forward to in the future even more opportunities.

Andrew Schorr:
Right. I know we've talked to patients who are on therapies that are working for them and they hope, you know, every day they wake up that it's still working, and they hope that it's a bridge to what's next.

Dr. Carbone:
What's next, yes.

Andrew Schorr:
And that's a way to look at it now that there is a what's next in many of these areas, right?

Dr. Simon:
That's exactly right. I think in terms of fighting cancer, knowledge is power. The more you understand about the tumor the better off you are. So I think it would—the patient should sort of ask their oncologist, have you worked up my cancer fully at the molecular level? And also they should ask their oncologist, are there any good clinical trials for me? Because sometimes a clinical trial is the best way to get a novel, new drug which may not be FDA approved and otherwise not available.

Andrew Schorr:
Tomorrow's medicine today.

Dr. Carbone:
Exactly. Tomorrow's standard of care is the clinical trial of today.

Andrew Schorr:
Right. Right. Well, there are some clinical trial finders. We have one on our website, patientpower.info. There is information through the Patient Empowerment Network. So be sure to use this and draw on some of the wonderful patient advocacy groups to guide you as well so that you can connect with that.

I want to thank you gentlemen for being with us. We will continue this discussion on lung cancer. Dr. George Simon from MD Anderson, thank you for all you do down in Texas. And in Ohio, thank you so much, Dr. David Carbone, for being with us.

Dr. Carbone:
You're welcome.

Dr. Simon:
Thank you.

Andrew Schorr:
I'm Andrew Schorr. I want to thank you for watching this Patient Empowerment program, and I want to thank our supporters, Pfizer, Genentech and Celgene. Remember, knowledge can be the best medicine of all.