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NSCLC Therapy Management and Biomarker Testing

**Introduction:**

Welcome to CME on ReachMD. This activity titled NSCLC Therapy Management and Biomarker Testing is provided by AXIS Medical Education, and is supported by educational funding provided by Amgen. This replay of a live broadcast focuses on newer therapies on the horizon for advanced or metastatic NSCLC patients with targetable mutations. Now, here's your moderator, Dr. Mark Socinski.

**Dr. Socinski:**

Hello, everybody and welcome to this activity today. If we can show the first slide, we will see the title of the program here. This is my name and title, Executive Medical Director of the AdventHealth Cancer Institute in Orlando, Florida.

Next slide, please.

Now, during this discussion, this is just a disclaimer and disclosure that we may be discussing some off-label use of either approved or newer agents that are in development. So if we do, we will certainly point that out.

Next slide, please.

These are my disclosures for conflict of interest.

Next slide, please.

In the agenda for today is summarized here, we'll just overview some of the key oncogenic drivers, we'll run through the W's of molecular testing and why it's important, what's new in the area of targeted therapy after frontline therapy, we're going to focus on that space today. We've got a case study, to watch with some audience response questions, some key takeaways, that I'll summarize, a Q&A session, as well as the post assessment questions. So that's the plan for the next hour.

Next slide, please.

So the objectives are shown here and, upon completion, the participants should be better able to identify a few key oncogenic drivers in non-small cell lung cancer, integrate guideline-recommended strategies for biomarker analysis specifically in advanced stage disease; this is a process that we identify efficacious targeted therapies, evaluate the various biomarker testing, methodologies, and diagnostic assays. We'll assess some new evidence for the newer targeted therapies in IO options in these populations, and then apply some evidence-based biomarker-guided therapy for advanced disease based on the presence of the oncogenic driver mutations.

All right, next slide, please.

So the overview, and we'll skip to the next slide, which kind of paints the big picture of lung cancer. We know that lung cancer, in my opinion, is public cancer enemy number 1, it is the most common cancer in the world, and most responsible for the greatest number of cancer-related deaths. In fact, you can combine the deaths from the other 3 big solid tumors, prostate, breast, and colorectal cancer and still not get to the number of lung cancer deaths that we see worldwide. Three people die every minute from lung cancer.

Next slide.

So we've seen quite a evolution, if you will, in terms of disease that started in an era of kind of one size fits all, to a very heterogeneous disease that's genomically defined as well as defined by PD-L1 status nowadays. Obviously, the first big step years ago was differentiating non-small cell from small cell because of its different behavior and management strategies. Two drugs forced us to further subdivide the non-small cell into essentially squamous versus non-squamous, that was bevacizumab because of the risk of toxicity. And pemetrexed, based on efficacy issues being ineffective in squamous patients. So that drove that histological distinction between squamous and non-squamous.

And then, almost 20 years ago in 2004, with the identification of EGFR mutations, we've seen a number of driver mutations that have really changed the standard of care and the first-line setting and really demand comprehensive genomic testing to identify the current 5 mutations and 4 fusions in which we have FDA approved therapies for, based on better efficacy with targeted therapies versus standard chemotherapy, with or without IO therapy. So it's important to understand that this now has become a very heterogeneous disease and a disease that really is defined by assessing the genomics of the cancer.

Next slide, please.

This kind of points that out. This is looking at the pie diagram. In non-squamous non-small cell lung cancer, we understand that most of non-squamous is adenocarcinoma, and I mentioned EGFR at one point on the previous slide. And you can see to the left here that we've seen a number of either other mutations, things like HER2 mutations MET exon 14 splice mutation, BRAF mutation mutations, and then the fusions that are noted there, ROS1, RET, ALK fusions are important to identify. And so this disease that looks like an adenocarcinoma under the microscope really meet - needs to be defined genomically to really allow optimal management of this population of patients.

Next slide.

So here's the scorecard, if you will. And again, I've mentioned the kind of 5 mutations and 4 fusions that we have shown here. And you can see that many of these the majority of them actually have approved therapies in the first-line setting, 3 of them the EGFR, exon 20 insertions, KRAS, G12C, and HER2 positive disease are - currently have targeted agents in the second line setting following platinum-based chemotherapy, of course, with or without IO, or with or without anti-VEGF therapy in that setting. And obviously, after exhaustion of the targeted therapy effect, many of these patients are eligible to receive platinum-based chemotherapy following disease progression.

So again, you see, in many of these boxes, there are a number of different choices, it's become quite complicated. And it's nice to have options for this population of patients. The bottom line is, many of these drugs have fantastic activity, as I'll show you subsequently. And you can't use them unless you do the comprehensive genomic testing to identify the genomic alteration.

Next slide please.

The W's of why the test and how it affects the guidance of treatment.

Next slide, please.

Well, who needs molecular testing? Every – the only issue is histology. We should not be using clinical factors, patients with non-squamous non-small cell or non-small cell not otherwise specified. This is from the NCCN clinical practice guidelines, should be tested, patients with squamous cell if they are light smokers, never smokers, if you have a small biopsy specimen, or mixed histology, small biopsy specimens may be hard to make a histology call. So I would always err on the side of doing more testing versus less testing. And I find myself in my practice testing more and more squamous cells, based on some of these factors shown here on this slide.

Next slide, please.

Now, what molecular targets should you be testing for it? And again, I would argue that anything that has an FDA approved targeted therapy, that target should be evaluated at the time of diagnosis. You can see in Stage IV disease, the NCCN guidelines recommend the full panel of all 10 biomarkers in these patients without adeno, and considered for squamous cell. Broad panel testing is recommended. Where possible, I think we pass the era of single gene testing. Typically, the best broad panel, I'll show you a slide on this in a moment, is next generation sequencing based optimally DNA RNA based. We do have an indication for osimertinib in the early stage, surgically resected population, and those patients that have EGFR mutations. So certainly EGFR testing, I guess that's the one argument you could make for single gene testing, since there's only a single FDA approval at this point in this population of patients. But I think otherwise it's the full panel in advanced stage disease.

And here, another key point you should know all the results of the molecular testing before you make an initial treatment decision.

Sometimes that takes coaching the patients a little bit to wait another week or several days to get those results. I always say that the biggest impact we make in Stage IV non-small cell lung cancer is what we do first. You're not always guaranteed that you're going to get in second line. And therefore, you ought to make the best and proper choice, kind of following the paradigm of right treatment with the right patient at the right time. So that's, that's a take-home message there.

Next slide, please.

Again, when to test? I kind of alluded to this. This should be at the time of diagnosis. You know, all of these 10 biomarkers in my mind are this equivalent to ER/PR and HER2 in breast cancer. You know, we wouldn't make a treatment decision in breast cancer without knowing that. We should know it in Stage IV non-small cell lung cancer. I mentioned the testing of EGFR in the surgical patients, and also the I think there is a role for retesting at the time of disease progression. We're beginning to learn a lot about the acquired resistance patterns for these targeted agents and sometimes retesting at the time of disease progression can be informative in terms of what the subsequent treatment options may be for that particular patient.

The other thing here in – about the time of disease progression, is that sometimes the clinical course is highly suggestive of histologic transformation. So we biopsy to define the histology, is also important. So I'll just put that little tidbit in there. That's obviously a clinical judgment.

Next slide.

Which tests to use? As promised, I said I'd come back to this. So you can see here, the various options NGS, PCR, IHC, and FISH testing. NGS ,optimally, I think is best as that's often DNA and RNA based and not everyone is RNA equipped, but you should have whatever you're using for testing, one should ask that question, it does optimize the identification of fusions. PCR does cover a lot of these but is dependent upon the primer so may miss some of these, this is most evident in the EGFR exon 20 insertions where you will miss the majority of them with PCR-based testing. IHC, which is protein expression can have some role certainly in ALK and ROS1, there's a role for it in that setting. Obviously, PD-L1 is immunohistochemistry based. So you're looking at protein expression. And FISH does – historically has played a role, but I think that's a difficult methodology. And even though it can have a role, I think it's rather limited at this time.

Next slide, please.

Don't forget about plasma. You know, I think plasma and tissue are complementary. In my practice, I – in the vast majority of patients, I do both. So kind of parallel testing, if you will. The plasma testing is a faster turnaround time. Certainly useful when you have limited tissue, and t does identify the biomarkers as adequately as tissue does. If you find something in the blood, you can believe it, you can act on it, and the outcomes with regard to response rate seem to be the same. The NCCN guidelines do recommend it in certain circumstances. Medically unfit for invasive biopsy in sufficient material or if the tissue-based testing did not cover all of the actionable recommended biomarkers.

So we have plenty of validation studies, the NILE trial, the studies out of UPenn, the trial from the UK, all show that, in my opinion, that this is a valid approach with clinical utility that complements tissue-based testing. So it is part of the everyday practice of oncology at this time.

Next slide, please.

So one has to take into account choosing the optimal diagnostic approach and methods, you know, how often are you going to anticipate that you're going to get a diagnosis and get adequate tissue, the invasiveness and risk of the procedure from the patient's point of view, how efficient is it, how easy it is to access, and how quick is the turnaround time, and is the expertise available with regard to these things. Also many patient-specific factors. You know that the median age of lung cancer is 70 years, many people have a history of smoking, there's often comorbidities, the anatomy of the tumor may be such that the biopsy could be particularly risky. Are you going to get an adequate volume of tissue specimen to do everything that you need to do? And is the tumor viable at the proposed biopsy site? And sometimes PET can be helpful from that point of view. And these are the things that we – I mean, in a perfect world, you would have a multidisciplinary discussion about this. Many of these things we talk about at our weekly tumor board and we make a decision with the interventional radiologists, the pulmonologists, the thoracic surgeons, these are the people that go and get tissue for us. And we'd like to do one thing to get all the tissue that we need. And again, I think it's best done in a multidisciplinary fashion if possible.

Next slide, please.

And the why? This comes back to the why. And these are a series of waterfall plots in various molecularly defined populations that got targeted therapy. Obviously, you can see the shapes of these waterfall plots are all the same. The vast majority of patients that have the

target, can get the targeted therapy, have significant tumor reduction. And that's the bottom line. Again, the goal here is to get the right treatment to the right patient at the right time.

Next slide, please.

Again, getting back to who to test. This slide just summarizes a bit of what we said on a previous slide, but just kind of updates the most recent 2023 NCCN clinical practice guidelines, test for all the targets is what the NCCN says. They also know that PD-L1expression is important to assess. Remember, PD-L1 expression is immunohistochemistry, so the turnaround time is you know in the range of 48 to 72 hours. The molecular testing may take longer. My advice is to ignore the PD-L1 result until you know the full molecular panel and make your decision at that point. Do not act on the PD-L1 status before you know the mutation or fusion status of the patient.

The NCCN also again mentions liquid biopsy as a testing option. In certain clinical situations the CAP Guidelines as shown here, they're a bit more historical and from 2018. But again, testing for the targets should be multiplexed. There are targets beyond EGFR, ALK, and ROS1, as we pointed out. They also say in some clinical settings, liquid biopsy for EGFR testing is an option if tissue is limited or insufficient. I think that was maybe true in 2018, I think it is unequivocally a standard of care to use liquid biopsy to test for all the targets at this particular point. So again, I think it's part of everyday clinical practice and 2023.

Next slide, please.

So what's new in targeted therapy after frontline treatment of non-small cell? Let's go to the next slide here. We're going to pick on the MET exon 14 skipping population here, and just show you some data from the CHRYSALIS phase 1 trial, not the exon 20 insertions that it's currently approved for, but remember amivantamab, which is summarized here, is bispecific antibody inhibiting EGFR as well as MET. There was a cohort in this study looking at the MET exon 14 skipping mutation. Again, this is a different approach than the TKI approach. Patients had to have obviously documented MET exon 14, either by NGS or circulating tumor DNA and measurable disease.

If we go to the next slide.

We see the monotherapy with amivantamab in this population had an overall response rate of about 50%. If you did not have a prior MET inhibitor, but if you were heavily pretreated with a prior MET inhibitor, the response rate was only 17%. The anti-tumor activity was somewhat durable. You can see that the longest respond around 276 weeks that was still ongoing at the time of this report. So some evidence of activity, either in treatment naive or previously treated patients.

Next slide, please.

The safety summary, of course, we know that one of the major issues with amivantamab is the infusion-related reaction. This is kind of a day 1 issue only.

After day 1, it really decreases in frequency. The other things such as rash, dermatitis, paronychia, and peripheral edema, again, these are common side effects; however, most of them are grade 1 or 2. You can look in the, either the larger population or the recommended phase 2 dosing of 425 patients and then the MET exon 14 skip mutation 55 patients, again fairly similar rates of toxicities. And again, from a grade 3 or higher point of view, most of them are single digits or, in fact, all of them are single digits for the most part with regard to high-grade toxicities. So specifically in the MET exon 14 skipping population, that there were no new safety signals in that population. Again, in addition to the day 1 infusion reaction, I'll also point out the risk of ILD with about 4% in the cumulative rash. Most patients had rash, but only about 4% had grade 3 or higher rash.

Next slide, please.

Again, switching gears to the exon 20 insertion population, this is the EXCLAIM trial that evaluated mobocertinib. This is the design, there were obviously multiple cohorts, did include a HER2 exons also in certain cohorts. Cohort 1 was the patients with prior platinum. There was an extension cohort shown to the bottom right. Again, these were previously treated patients with EGFR exon 20 mutations, which we know is again, a heterogeneous group of patients in and of itself.

Next slide, please.

The confirmed response rate was about 28%. So the remarkable thing about the responses is the durability of the response. You can see a median duration of response of 17.5 months, median PFS of just over 7 months, and median survival of about 2 years in this study. So again, lower response rates, but durable responses. And obviously it begs the question, who is that 28% of patients that are having these very durable responses? And what's different about them compared to the patients that don't enjoy a response? And I think that's one of the outstanding questions which will hopefully have some clarity of data moving forward, as we study this very heterogeneous population of exon 20 insertion patients.

Next slide, please.

Of course, the major issue we see with mobocertinib is diarrhea. You can see the rate of grade 3 treatment-related adverse events about slightly shy of half the patients. About 17% led to discontinuation, about 25% led to dose reduction. The most common AEs leading to discontinuation or GI in nature, nausea, vomiting, diarrhea, anorexia, stomatitis, these sorts of things. So important to be aware in be prospective about managing the toxicities prospectively.

Next slide, please.

Again, looking – switching gears. This time, we're back to our table of the 10 big ones here. We're going to talk about the KRAS G12C population.

Next slide, please.

We have two approved agents, and you can see the dates that they were approved, to the left sotorasib, to the right adagrasib. You can see the response rates to both of these agents are just south or just north of 40%; 37% for sotorasib, 42.9% for adagrasib. The disease control rate, median duration of response, PFS data, and overall survival data are remarkably similar. You see the waterfall plots also are very similar in shape.

Next slide, please.

That data that we just showed you from the sotorasib point of view was essentially CodeBreaK100. You can – so I mentioned the response rates there. But we know in the second-line setting that docetaxel has remained a suitable standard of care and is accepted by the FDA as a control arm for randomized phase 3 trials. And the data from CodeBreaK100 that we showed you on the previous slide was the basis for CodeBreaK200, which essentially compared sotorasib to docetaxel in the second-line setting in previously treated KRAS G12C mutated advanced non-small cell lung cancer.

Next slide, please.

This is the design. You can see again, they had to have at least one prior treatment that had to be platinum-based chemotherapy and a checkpoint inhibitor, good performance status, randomized between the control arm of docetaxel which is perfectly appropriate. There it is given at the FDA approved dose and schedule 75 mg per meter squared every 3 weeks. And then sotorasib was the investigational arm given that the standard dose of 960 mg orally daily. The primary endpoint was progression-free survival. This was assessed by a blinded, independent review committee.

If we go to the next slide, it will show you the primary endpoint, which again was PFS by the blinded radiology group. You can see this did meet its primary endpoint with a hazard ratio of 0.66, the 12-month PFS rate was 25% for sotorasib, and 10%, so 2.5-fold difference compared to docetaxel. Overall survival was a secondary endpoint, it did not show a difference, but again, it was a secondary endpoint in this trial.

Next slide, please. Here are the common grade 3+ treatment-related adverse events with both agents, sotorasib and diarrhea. Most commonly with sotorasib were elevated liver enzymes and diarrhea and with docetaxel, as one would expect, it's more of a myelosuppressive neutropenia, neutropenic fever, as well as fatigue. So very different toxicity profiles of these two agents.

Next slide, please.

Adagrasib was evaluated in the KRYSTAL-1. Here is the phase 2 design. Again,
600 mg BID. These were previously treated patients with a platinum-based chemotherapy and PD-1, PD-L1 inhibitor. Again, the primary endpoint was overall response rate.

In this trial, if we go to the next slide, it will show us the progression-free survival to the left of 6.5 months and the overall survival to the right, median survival was 12.6 months. And as I mentioned on one of the introductory slides to the KRAS section here, the overall response rate was 43% in this setting.

Next slide, please.

The treatment-related adverse events again, mostly GI related but mostly grade 1 or 2 nausea, vomiting, diarrhea, some liver function abnormalities, some creatinine abnormalities. Again, the treatment-related adverse events led to discontinuation in 7% of patients, dose reduction in 52%, and dose interruption in 61%. Again, most of these were grade 1 or 2.

Next slide.

Lastly, we're going to focus on HER positive. This is HER mutations, and look at the data with trastuzumab deruxtecan.

Next slide, please.

Here we have the DESTINY-Lung02 study design shown here. This was a phase 2, two-arm, multicenter, randomized but non-comparative trial. It was specifically done in HER2 mutated non-small cell lung cancer that had had previous platinum-based chemotherapy. It did have measurable disease, two dose levels of trastuzumab deruxtecan were evaluated, the lower dose and 5.4 mg/kg every 6 weeks and 6.4 mg/kg every 6 weeks. Again, it was not necessarily designed to compare the two but just to observe the outcomes on both arms. The primary endpoint was overall response rate by blinded review, and you can see the secondary endpoints shown to the bottom left.

Next slide, please.

Here's the response rate based on the arm. And you can see for the lower dose of 5.4, the confirmed response rate of slightly shy of 54%. And on the higher dose, 43%. Again, it's not meant to compare the two doses, but just to observe what the response rates were since that was the primary endpoint. And you can see the median duration of response had not been reached on the lower dose, was about 6 months on the higher dose. This study is – was at the time of this recording was relatively early. But the conclusion here was there didn't seem to be advantage – a great advantage for the higher dose. We're not saying the lower dose is better, but the lower dose seems to be an adequate dose. And there didn't seem to be any rationale for using the higher dose.

Next slide, please.

The safety is shown here. And again, like you see with many of these agents, remember, trastuzumab deruxtecan is an antibody drug conjugate, the payload is deruxtecan which has chemotherapy-like or cytotoxic properties and so you see some myelosuppression with neutropenia, anemia, these sorts of things. Also some GI toxicity. Again, the vast majority of it is grade 1 or 2, but you do see a little bit particularly with regard to myelosuppression neutropenia, 15% grade 3, 3% grade 4, and a little bit anemia 10% grade 3. Otherwise, the toxicities seem to be largely grade 1 or 2.

The next slide, please.

So that completes what we wanted to review from the targeted therapy point of view. I wanted to share a case study with you. This is actually a lady that I've cared for over the past several years.

Can we go to the next slide?

Now, those of you – we have some audience response questions here, so either set up your laptop or set up your phone so that you can participate in the audience response part of this because we'd like to get as many responses as possible.

For all your Yankee fans out there, here's to you. Perfect game last night, New York Yankees.

An 82-year-old woman, never-smoker, presents with a persistent cough. Gets a chest CT, shows a 5-centimeter right upper lobe mass. She does have ipsilateral mediastinal adenopathy. PET scan shows only intrathoracic disease that we saw on the chest CT, she had a negative brain MRI. It was felt that her best diagnostic approach was a mediastinoscopy. That was done. She had multi-station disease and 2 out of 4 on her station 7 with adenocarcinoma. We did do molecular testing, broad based, and she had a KRAS G12C mutation in this setting. She didn't have much in the way of medical. She's a pretty robust 82-year-old. We see a lot of those in Florida. She had been widowed for 5 years, she had a couple of kids living closely, and she was retired. She had no family history of cancer.

Next slide.

So her stage was a T3, N2, or a Stage IIIB. She was initially treated with concurrent chemo-rad. So weekly carbo-taxol. Did transition to consolidation durvalumab. But about 3 months into her course of durvalumab, she had a follow-up CT scan that showed multiple new bilateral pulmonary nodules.

Next slide, please.

So with that finding, and of course I didn't show you the CT but you can trust me that there were multiple bilateral, what would you do at this time? What would you recommend? A repeat biopsy? Would you do plasma-based next generation? Or would you just assume this is disease progression and then move on to whatever your next line of therapy was?

So we'll give people a moment to record their what would you do at this point? And the majority here repeat biopsy, one plasma-based next generation testing. Let's - I guess we've allowed enough time, let's move on to the next slide.

Well, we did do the majority wins here. We did do a repeat biopsy. You can see the repeat biopsy showed adenocarcinoma and had the same KRAS G12C mutation that she had at initial time of her diagnosis. So we felt that this solidified the diagnosis so solidified that she

was now Stage IV. And we obviously stopped the consolidation immunotherapy.

Next slide, please.

So at this point, what would you now recommend? Platinum-based therapy? Platinum-based therapy plus I guess a different IO agent? Would you move on to traditional second line docetaxel, ramucirumab? Or sotorasib or adagrasib?

Okay. We've got now in equals, but we got some uptake of sotorasib in this setting. All right. I don't –

Okay, we can go to the next slide.

I don't know. As you know, as I was putting together these questions, I don't know that there's necessarily a clearly favorable or correct answer. I can tell you, I'm going to say that my answer was the correct answer. So we'll leave it at that. But at the time, you know, she - I considered her first line Stage IV. She had an adenocarcinoma, she had not received pemetrexed-based therapy at this point. I did not see a role for adding any other IO agent at that time since she had progressed on durvalumab, and I did not think she was a candidate for anti-VEGF therapy largely because of her age. We know that the side effects of bevacizumab do increase - I used to - I tell my trainees think twice about giving over the age of 75, and think three times giving it over the age of 80. So I did not opt for the use of bevacizumab. So we treated her with carbo-pemetrexed. And she got 4 cycles, she had a response. And she transitioned to maintenance therapy, which she tolerated pretty well. And that bought her about 11 months without much in the way of toxicity. But follow-up CT scan now shows that the nodules she did have were increasing and she had some new ones. And again, at this point she was somewhat symptomatic from the chest disease.

So if we go to the next slide.

So now we've completed almost a year of this, what would you do now? So you see the choices here, docetaxel/ramucirumab, sotorasib, adagrasib? Or is there some other option that you would choose?

Okay, we've got a majority of you saying the targeted agent, sotorasib. In a very strong minority, docetaxel/ramucirumab.

Let's go to the next slide.

So at this point, I chose sotorasib. Obviously, you know, you're right, docetaxel with or without ramucirumab is an option. I figured at this point, she had a target, G12C KRAS, we had an agent, sotorasib, and that's what we went with. I felt that the side effect profile in this now woman who was 85 at this point I think, would favor sotorasib versus docetaxel. And again, I didn't want to give her bevacizumab in the first-line setting, so I didn't necessarily want to give her ramucirumab in the second-line setting when she was 3 years older than when I first met her. So she started on sotorasib and had very little or no toxicity in her age group. I was a little worried about the GI aspect of it. But she did well. She confessed every time I saw her that she was taking all 8 pills every day. She didn't like it, but she said she took them all. Minor response on CT scan. I'm not quite sure if she would have met RECIST criteria, but she felt better. So that was what we were aiming for. And she so far has been on treatment for 19 months. So I considered that success and I haven't seen her in a month or so. So we'll see how things go as we – as her disease plays out. So I think that's the end of this particular case.

If we can go to the next slide,

Yeah, okay, so the key takeaways here. This is a very heterogeneous disease. A molecularly diverse disease, one size does not fit all. It is completely standard of care and necessary to do comprehensive genomic testing, in my opinion, using an NGS based platform that's DNA and RNA based, so that you find all of these targets. You should do this as early as possible, so that the results are available before you make your first-line treatment decisions. We do know that when you have a target, if you get a targeted therapy, you optimize the outcome of those patients. And don't forget about the fact that I believe tissue and plasma NGS testing are complementary. And there are certain advantages of liquid biopsy in terms of turnaround time, and certainly useful when you don't have adequate tissue, or all the – and all the targets weren't tested for, or can be helpful also at the time of disease progression.

So next slide.

All right, Q&A. Let's do some Q&A.

So we've had a number of questions that have been submitted, so I'll just kind of take them one at a time here. First question is, is EGFR overexpression used at all in deciding treatment? I'm going to assume that EGFR overexpression is looking at protein expression on the cell surface using immunohistochemistry. Today, it's not used routinely in making treatment decisions. You know, there were early studies looking at the anti-EGFR antibodies, cetuximab, panitumumab, and these sorts of things, looking was there a role for EGFR, IHC, and it really never panned out. And so currently, it's not used in the decision-making now. You know, we do have a number of antibody drug conjugates coming up. You know, we may see a resurfacing of immunohistochemistry for target identification, whether or

not there'll be useful biomarkers, only time will tell.

Next question, how do you decide between plasma and tissue-based testing? And are the results the same? Well, obviously, everyone gets a biopsy because we need to know the diagnosis and the histology of the patient. So you know, everyone gets tissue. That tissue usually is robust enough to do the testing; however, sometimes it's not. As I mentioned early on, I do plasma and tissue in all patients. And the reason I do that, is the validation studies, particularly the NILE trial, which was published several years ago, clearly showed the clinical utility of plasma-based testing at the time of diagnosis yielding about 20% more identifiable genomic alterations, than when you just rely on tissue. So again, I work from the position that the best thing or one of the greatest things we can do as an oncologist is to identify an oncogenic driver, because of the activity of these targeted therapies. So I do everything possible to try to identify them. And I do think that tissue and blood are complementary. Plasma is very useful at the time of disease progression. So that's what I typically do first, unless I do suspect histologic transformation. You know, there's a small percentage of small cell transformation. So you have to do a biopsy to identify those patients.

Next question is, are you at all concerned about cumulative toxicities and a potential for them when looking at combined modality treatment? Yeah. Yes. The short answer is yes. I think we pretty much understand the cumulative toxicities of combined modality treatment, and I'm assuming when you say ask the question, combined modality treatment, this is largely in the Stage III population where we're giving chemoradiotherapy, we understand that the primary toxicity there is esophagitis. Esophagitis is a disease in which 1 pound of prevention is worth 2 pounds of cure. This is something that you should manage aggressively, prospectively with pain meds, esophageal soothants, acid-reducing substances, Diflucan, a lot of this could be fungal infection, super infection. And I'm pretty aggressive at managing it so it doesn't become a major issue. The common toxicities to be aware of we - I mean, we covered most of these with this. I mean, obviously, there are so many agents that I showed you on that one slide with the 10 approved biomarkers and all of these agents, we don't obviously have the time to be aware of. One should become familiar with all of them if you're going to use these agents. There's a lot of overlap, and it largely has to do with GI and liver toxicity, some skin toxicity. Many of them have QTC issues, so you need to be aware of that in the appropriate patient. So - and then the question, do toxicities with targeted agents correlate with efficacy? That's an interesting question, because we've, you know, seen historically that, you know, in the early studies with first generation, EGFR, TKIs, that there was a correlation between overall survival and in rash. And so if you had a rash, you seemed to do better. We also noticed the development of hypertension with anti-VEGF treatments seemed to identify patients who did better with regard to overall survival. So there is some correlation. We've just published a paper in *JAMA Oncology* looking at immune-related adverse events, and they clearly, patients who have them seem to do better. So that's another observation about how toxicities may correlate with outcomes.

How does data in microbiome play with targeted therapies? You know, I'm not much of an expert on the microbiome. So I can't really address that question. I think it's an interesting question. I think it may be more important for the immun-ooncology drugs and the targeted therapies. But I would not accept my answer as the definitive answer.

Combining targeted therapies in immune checkpoint inhibitors is treacherous business. This was first identified when osimertinib was attempted to be combined with durvalumab, an anti-PD-L1 agent, and that study was stopped early because of an excessively high rate of pneumonitis. And we've also seen some issues with liver toxicities with the ALK drugs and IO therapy and stuff like this. So I think the party line is right now, is don't combine them outside of a clinical trial. And many of the TKIs do not play well with IO agents. I wouldn't say that's true of all of them. But until we know the safety, I would not combine them outside of a clinical trial.

Racial or ethnic differences, do they affect therapy choice? They – we know that there are disparities. We saw some interesting data concerning data at ASCO a year or two ago, looking at the rate of molecular testing, which was we know there's gross undertesting in the United States. And there were – the African Americans were less likely to get tested and less likely to get tested via an NGS platform. So I'm not sure that therapy choice. I think if you find something, I don't know that there's much of a racial difference between the therapy choice. I think the issue is in the diagnosis of these sorts of things based on race. And we know when documented disparities in the United States.

What message would you give community oncologists about the treatment of non-small cell with targeted therapies? The message I would give would be do - routinely do comprehensive genomic testing. I've heard from a couple of community oncologists who say, 'I test all the time, but I never find anything,' and I say, 'Perfect. The next patient you test is going to have something don't give up.' Again, many of these are in the 1 to 2%. Well, but if you add up - quickly in adenocarcinoma, if you add up all those 10 targets, then almost half the patients are going to have something that has an FDA approved targeted therapy now. You know, things like KRAS G12C, EGFR mutations, you're not going to find a ton of RET fusions or NTRK fusions and these sorts of things, but you'll occasionally find them. The point is, is that when you find them, these targeted therapies can make such a difference. The last patient I treated with a RET fusion, which was probably about 4 to 6 months ago, was a guy, a very fit guy, just retired early 60s, was an exercise freak, was at the gym every day, developed Stage IV RET fusion positive disease. He had a sacral MET on his left side, such that he could not exercise. I

mean, he could not bend over and touch his toes, because of the pain and stuff like this. And when I started him on selpercatinib, which is what I did, that pain was gone within a couple of days. That's how dramatic the response can be. So all you have to do is see one of these and see the dramatic response. We know that the targeted therapies work relatively quickly if you have one of these driver alterations. And so I think that this is the message to community oncologists, is continue to test, don't get testing fatigue. And if you test, make sure that you know the result, have someone in your office birddog the results, don't let it get shoved into a file somewhere where you might not see it. We do know that not every patient with a identified target gets a targeted therapy. There was a very nice poster at ASCO this year. Not a very nice poster, a very concerning poster, showing a certain percentage of patients with all of these alterations never got the targeted therapy. So it's not enough to test, you have to also act on the result of the test. So that's the take-home message, keep testing.

We've got one question here, in these patients with driver alterations, why don't we see higher response rates with targeted therapies? Well, in fact, we do see higher response rates. I showed that one slide I showed that showed all the waterfall plots. You don't see those sorts of waterfall plots with chemotherapy or IO therapy. So the question may be generated by the fact that, for instance, in the like with mobocertinib, the response rate was 28%. With the KRAS G12C drugs, the response rates were about 40%. Those are much more - the exon 20s in the KRAS G12C are much more difficult to target and to inhibit, and so that's why I think you see some lower response rates with those. What I'm talking about are the things like the RET fusions, the ROS1, ALK fusions, the EGFR mutations, the sensitizing mutations, the MET exon 14, all of which have response rates well north of 50%. And you just don't see that sort of response rate with chemotherapy, and this is not - these driver populations are generally not the type of patient that you see with - that they get much benefit from immunotherapy in this population.

Next question, can you use ctDNA to determine which agent in the class to use? At the time of initial diagnosis, probably not. There can be some helpfulness of ctDNA at the time of disease progression, for instance, in the ALK space, if you let's say you start off with alectinib, and then you know, 3 or 4 years later the patient progresses, you retest at progression, which I do, and let's say you find an acquired ALK resistance mutation that is resistant to alectinib, but may be sensitive to one of the other, or pacritinib, or ceritinib. So that can be helpful, but that's going to be a small minority of the patients. And again, one question about do you retest upon progression? Yes, I do. I will admit that it's probably informative only in a minority of patients, but sometimes your patient is in the minority of that and it can be helpful. Again, I think you have to be suspicious if the clinical progression is rapid, that there's histologic transformation. So I would biopsy first, so you can rule out the transition - transformation to small cell lung cancer. So that's it.

And then how do you work with a multidisciplinary team in the refractory setting? Not so much in the refractory setting. In the, you know, multidisciplinary input in the team is incredibly important. We have a weekly tumor board where all the disciplines are there. In fact, we don't start the meeting until all disciplines are there. And we debate back and forth between the disciplines about various issues in the management of patients. Usually it is at the time of initial diagnosis. At the time of disease progression or the refractory setting, that's usually the land of the medical oncologists trying to decide what to do. Now, many times, we may want to do a repeat biopsy, I will bring the case back to the tumor board, and I will ask my colleagues that do these sorts of biopsies, what do we think is the safest and best way to get a biopsy and a diagnosis for what I'm looking for? And so that's where the multidisciplinary team in the refractory setting can be helpful. So that's where I would bring back the multidisciplinary team in this particular case.

Shared decision-making is a question here when choosing therapy. I use that phrase a lot when I talk to patients. And I think, even though I use it a lot, and I say this is a partnership, at the end of the day, the patient's going to look at you and say, ‘You're the expert. What do you think I should do?’ And I think that's kind of kind of how we ended. And then I give them my recommendation, but at least I think we've had this discussion.

So we're getting to the end of our time here. This has been great, at least from my point of view. I've enjoyed the discussion, enjoyed the audience response questions in the case that I shared with you. I hope that I've impressed upon you that this is not your father's lung cancer. I've been a lung cancer doctor for 30 years. And sometimes I sit back and think about how different the management of lung cancer is today than it was in 1993, where we actually debated as to whether or not lung cancer was a treatable disease. It demands comprehensive genomic testing. It's become the poster child for targeted therapies as well as immunotherapy in the first-line setting. We're seeing survival statistics that we've not seen in the past. When you look at the year 2017, it was the year that we saw the greatest reduction in cancer mortality in the United States that had ever been reported in the two diseases that led the way in reduction of cancer mortality were lung cancer in melanoma, historically two difficult diseases to treat. But nowadays, both diseases that are poster children for targeted therapies and immunotherapy. The scale that we need is to get the right patient to - the right treatment to the right patient at the right time. So that's what you have to do. And that's the message that I'll leave you with. Thank you very much for joining me today. And I hope this was helpful and useful in your day-to-day practice.

**Conclusion:**

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