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Released: 05/26/2017

Valid until: 05/26/2018

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What the Experts Are Talking About: Advances in Immune Checkpoint Inhibition for NSCLC Therapy

Narrator:

Welcome to CME on ReachMD. This segment, What the Experts Are Talking About, Advances in Immune Checkpoint Inhibition for NSCLC Therapy, is provided by Vindico Medical Education and is supported by educational grants from Genentech, Incorporated and Merck & Company, Incorporated.

The activity moderator for today's program is Dr. Naiyer A. Rizvi, Professor of Medicine and Director of Thoracic Oncology and Co-Director Cancer Immunotherapy Program at Columbia University Medical Center in New York City, New York. Dr. Rizvi is joined today by Dr. Leora Horn, Associate Professor of Medicine and Director of Thoracic Oncology Research Program at Vanderbilt-Ingram Cancer Center in Nashville, Tennessee. Prior to beginning the activity, please be sure to review the faculty's financial disclosures. Please review the learning objectives for this activity. Upon completion of this educational activity, participants should be better able to implement effective treatment strategies for patients with NSCLC, based on knowledge of patient biomarkers and the most recent clinical evidence regarding the use of immune checkpoint inhibitors, and monitor patients undergoing immune checkpoint inhibitor-based therapy for immune-related adverse events and adjust the care plan accordingly.

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Here is your activity moderator, Dr. Naiyer A. Rizvi.

Dr. Rizvi:

Hello and welcome to, What the Experts Are Talking About, Advances in Immune Checkpoint Inhibition for Non-Small Cell Lung Cancer Therapy. I am Dr. Naiyer Rizvi, Director of Thoracic Oncology and Co-Director of Cancer Immunotherapy Program at Columbia University Medical Center in New York, and I am joined today by Dr. Leora Horn, Director of Thoracic Oncology Research Program at Vanderbilt-Ingram Cancer Center in Nashville, Tennessee. Within this CME activity we will be discussing effective treatment strategies for the care of patients with non-small cell lung cancer through evaluation of the most recent clinical evidence regarding the use of immune checkpoint inhibitors, consideration of biomarkers, and the identification and effective management of immune-related adverse events. Let's start with a polling question. Your 70-year-old male patient is diagnosed with metastatic non-small lung cancer. A biopsy reveals adenocarcinoma of the lung with no EGFR mutations, no ALK translocations, and PD-L1 expression of 10%. He was initially treated with combination cytotoxic chemotherapy with a platinum doublet, but received no response after 4 cycles of therapy. Which of the following would be the most appropriate next therapy for this patient? Pembrolizumab, nivolumab, or atezolizumab would be answer A. B would be ceritinib or erlotinib. C would be erlotinib or gefitinib; D, bevacizumab or ramucirumab.

So, in a patient such as this, who has progressed after first-line chemotherapy and has no druggable oncogenic driver mutation such as EGFR mutations or ALK rearrangements it would be appropriate to consider immunotherapy as the next line of treatment, there are now 3 immune checkpoint inhibitors approved for metastatic lung cancer. Pembrolizumab is approved as first-line therapy in patients who are more than 50% PD-L1 positive, which does not apply to this patient. It is also approved for patients with more than 1% PD-L1 expression in second line or greater setting, and both nivolumab and atezolizumab are approved in the second-line or greater setting in

unselected patients with non-small cell lung cancer. So, in a patient such as this who has 10% PD-L1 expression, either pembrolizumab, nivolumab, or atezolizumab would be appropriate options. We would not consider a targeted therapy such as alectinib or erlotinib for patients such as this where we have good treatment options and the patient does not have an oncogenic driver aberration that's present.

So, I will turn it over to Dr. Horn who will provide an update on current landscape of treatment options for non-small cell lung cancer with immune checkpoint therapy, as well as touch upon the potential toxicities that may occur.

Dr. Horn:

On this slide is a list of the current FDA-approved immune checkpoint inhibitors. Ipilimumab was the first immune checkpoint inhibitor approved. This was initially approved in patients with metastatic melanoma, and there is no current indication in patients with non-small cell lung cancer. Nivolumab and pembrolizumab were both approved in 2015 in the second-line setting for patients with Stage IV non-small cell lung cancer. And atezolizumab and pembrolizumab were approved in 2016; atezolizumab for patients as second-line therapy and pembrolizumab as first-line therapy in patients with Stage IV disease. In the next few slides, we'll go over the data that supported approval of these agents in each indication.

This slide is a summary of the clinical trials that led to approval of nivolumab, pembrolizumab, and atezolizumab in the second-line setting. All 4 trials had very similar study designs. They were randomized Phase III trials and the trials with nivolumab and atezolizumab compared these agents to docetaxel in all patients who had progressed following platinum-based chemotherapy. KEYNOTE-010 was the exception, as it compared pembrolizumab to docetaxel in patients with tumors that were PD-L1 positive in greater than 1% or more tumor cells. As you can see from the data, all 4 studies showed a very similar median improvement in overall survival, from anywhere from 2 to 5 months for patients treated with a checkpoint inhibitor, compared to docetaxel chemotherapy. And as a result, all 3 agents received FDA approval. Now, the difference in the CheckMate 017 and 057, compared to KEYNOTE-010 and OAK trial, is CheckMate 017 was a trial for patients only with squamous cell non-small cell lung cancer, and CheckMate 057 was only for patients with non-squamous non-small cell lung cancer, while KEYNOTE-010 and OAK trial enrolled both squamous and non-squamous non-small cell lung cancer patients.

The one area that's been somewhat confusing to breakdown for patients is the differences in PD-L1 expression that has been compared between studies, as well as the different antibodies that have been used. And this slide is really a summary of the different agents, looking at both response and survival for patients treated with each checkpoint inhibitor. And what you see on the top chart is, for patients treated with nivolumab and with squamous cell non-small cell lung cancer in the CheckMate 017 trial, PD-L1 expression did not appear to predict for response to nivolumab, and it also did not appear to predict for survival for patients treated with nivolumab, in that there appeared to be a benefit in response and survival in patients treated with nivolumab, regardless of PD-L1 expression. However, when you look at the non-squamous data with nivolumab, we see that PD-L1 expression does appear to predict for response as well as survival, with an almost tripling of response in the patients who are PD-L1 greater than 1%, compared to less than 1%, and that is also true for patients who are greater than 5%, compared to less than 5%, or 10%, compared to less than 10%. We also see a difference in response for patients treated with pembrolizumab based on PD-L1 expression with a higher response rate seen in patients who are PD-L1 greater than 50%, but you need to remember that the patients who are included in the analysis, the PD-L1 greater than 1% where we see a response of 18%, that also includes the patients who are greater than 50%, because it's all the patients who are 1% or more. With atezolizumab, at the bottom, we also see that PD-L1 expression appears to predict for response to atezolizumab. And there's a slightly different scoring analysis that is used for atezolizumab, where patients are not only looked at their tumor cell expression, but we're also looking at expression of the immune infiltrate. And so, on the right-hand side, the patients who are TC0 where a response rate is seen of approximately 8%, compared to the patients who are TC3 or IC3 where the response rate to atezolizumab is 42%. And also, a trend to an improvement in overall survival, although the overall survival from this data for patients who were either TC0 or, in the case of nivolumab, PD-L1 less than 1%, we still see a significant improvement in overall survival, compared to chemotherapy for patients treated with these agents.

There appears to be one group of patients who do not appear to have a significant benefit from the checkpoint inhibitors and this is the patients who are EGFR-mutant positive or ALK-rearrangement positive, or the never-smoking population. And this is a retrospective review of a cohort of patients who were treated with checkpoint inhibitors, and what you can see is, for the patients who are EGFR or ALK positive, the response rate to the checkpoint inhibitor is fairly low at around 4%, compared to those patients who are wild type where the response to checkpoint inhibitors, what we generally see with this agent, ranging from around 20%. We can also see that the never- or light smokers who are also those who are more likely to be EGFR or ALK positive, the response rate to checkpoint inhibitors is low at 4.2%, compared to those patients with a heavier smoking history where the response rate is again around 20%.

Now, as I mentioned, pembrolizumab has approval as well in the first-line setting and that's based on the data that was presented at ESMO last year from the KEYNOTE-021 study. And this trial compared first-line pembrolizumab to carboplatin and pemetrexed in

patients with Stage IV non-small cell lung cancer. And at the interim analysis, the study was actually discontinued early at the recommendation of the data safety monitoring committee, because of the significant improvement in progression-free survival for patients treated with first-line pembrolizumab, compared to chemotherapy, where progression-free survival was 10.3 months, compared to 6 months for patients treated with chemotherapy. At the same time as that data came out, there was a similar study run in patients, first-line study, in patients with Stage IV non-small cell lung cancer whose tumors were PD-L1 positive by greater than 1%, with an initial specified analysis for patients with tumors that were PD-L1 positive with greater than 5%, and those patients were randomized, again to platinum-based chemotherapy compared to nivolumab, and this study, however, did not meet its primary endpoint where we see there is no significant improvement for survival for patients treated with nivolumab compared to first-line platinum-based chemotherapy. There was a subset analysis performed on this data that looked at patients with tumors with PD-L1 expression that were greater than 50% that also did not show any significant improvement for patients treated with nivolumab compared to platinum-based chemotherapy. And so, therefore, at this time, the only checkpoint inhibitor that is approved, in the first-line setting, is pembrolizumab and that is for patients with tumors that are PD-L1 positive in greater than 50% or more of tumor cells.

So, we saw some interesting data at ESMO, as well, with combination therapy with carboplatin and pemetrexed with pembrolizumab, compared to carboplatin and pemetrexed alone, with a significant improvement in progression-free survival for patients treated with combination therapy as well as an improvement in response rate. There is a confirmatory ongoing Phase III trial comparing chemotherapy with carboplatin and pemetrexed as well as pembrolizumab compared to carboplatin and pemetrexed alone. Dr. Rizvi, has this data led you to use this regimen at all? What were your thoughts on the results?

Dr. Rizvi:

I think that one of the concerns around this data with first-line pembrolizumab plus chemotherapy is there was no overall survival advantage, certainly at the time of this presentation and publication. I think the second concern is what is the differential effect with adding chemotherapy in PD-L1 positives versus negative patients, which we don't know from this data as it was a relatively small study. And, finally, I think the unknown is what is the impact of the combination in terms of long-term durable benefit? We have now, data both at 3 years and 5 years, with single-agent PD-1 therapy showing a substantial tail on the curve, suggesting patients experiencing durable outcome cannot be recapitulated with the chemotherapy combinations.

Dr. Horn:

I agree with everything that you've said. I think one of the key pet peeves that I have is that there are a lot of studies that are currently ongoing with a very similar design, and none of those studies have a checkpoint inhibitor alone. And so, it may not be until 5 or 6 years that you actually see the benefit, or the true survival data, that these combinations may impact. And so, I guess, time will tell, both for the combination as well as the crossover arm.

The other combination that people are talking about a great deal is the combination of nivolumab and ipilimumab in the first-line setting. This was initial data as well from the CheckMate 012 study that looked at different doses schedules of ipilimumab with nivolumab and the dose of nivolumab in these trials was 3 mg/kg. Now a lot of these agents have moved to fixed dosing, 240 mg every 2 weeks for nivolumab, and then it looked at ipilimumab once every 12 weeks as well as once every 6 weeks, compared to nivolumab alone. And the preliminary data looks interesting, showing an improvement in response for combination nivolumab and ipilimumab, compared to nivolumab alone, as well as a potential improvement in survival, although this data is still not fully mature. The big concern that I have with the combination regimen is the increasing toxicities when you do combine a PD-1 or PD-L1 inhibitor with a CTLA-4 inhibitor, you're definitely seeing more of the toxicities that we're accustomed to with these agents. So, higher risks of colitis and pneumonitis as well as pan-hypopit, than you might see with patients treated with a checkpoint inhibitor alone. Nevertheless, there are ongoing Phase III trials comparing nivolumab and ipilimumab compared to nivolumab alone, or chemotherapy with nivolumab or chemotherapy alone. And there's also the MYSTIC trial that is comparing durvalumab, a PD-L1 inhibitor, with tremelimumab, a CTLA-4 inhibitor, compared to durvalumab alone or chemotherapy. And we may get some data from MYSTIC potentially later this year.

Dr. Rizvi:

Yes, I think that there are definitely different camps in terms of what they think the best first-line option is going to be. I think that for patients who are PD-L1 positive more than 50%, I think that pembrolizumab is an effective therapy, but the response rate is in the range of 50%, and I think the durable response rate is somewhat less than that. So, is there an opportunity to improve that subpopulation that are PD-L1 positive with a combination, whether it's chemo-combination or with immunotherapy combinations, and I think, conversely, what to do with the patients that are PD-L1 negative. Shall we approach those differently? I think that there's certainly a chance that PD-L1 testing will go away and everyone will just get chemotherapy and immunotherapy combinations, given the readout of Phase III trials this year, but I think that there still will remain a role for PD-L1 testing and selection for positive patients where immunotherapy alone seems to have a durable benefit.

Dr. Horn:

When you discuss the roles of PD-L1 testing, do you have a favorite assay or antibody that you are using or recommending?

Dr. Rizvi:

Well, I think that the antibodies which are in the clinic at present include the Merck 22C3 assay which is a true companion diagnostic to make a treatment decision, or for patients particularly in the first-line setting. And then the other antibodies are the BMS's 28A clone and Roche's SP142 clone. I think that, in general, given the outcomes to first-line pembro use are linked to the Merck assay, I think that the standard of care really should be testing with the Merck assay.

Dr. Horn:

That's what we're doing at our institution right now as well.

So, as you mentioned, there are multiple ongoing trials that are potentially going to readout this year and this is a list of some, although may not include all. The MYSTIC, as I mentioned, looking at durvalumab and tremelimumab. There are the EMPOWER trials that are looking at chemotherapy with or without atezolizumab and then the CheckMate 227 which is looking at combination nivolumab as well as ipilimumab.

So, I mentioned previously that various agents are not without toxicities and management of these toxicities can sometimes be a challenge as they are not always recognized. And so, if it ends in "itis," these drugs are known to cause it, and some of the toxicities that we think of -- so a patient coming in with extreme fatigue, we always need to think about hypo or hyperthyroidism as well as patients potentially having adrenal insufficiency and then there's also the risk of pan-hypophysitis. The skin toxicities appear to be the most common; patients noticing a little bit of pruritus or rash from these agents. The gastrointestinal toxicities and pulmonary toxicities appear to be not quite as common, about 2 to 3% of patients experiencing either colitis or pneumonitis, the latter which can be life-threatening if it goes unrecognized or treated as a pneumonia rather than a pneumonitis. And then, recently, there have also been reports of these agents causing myocarditis and death as a result of myocardial failure for patients treated with checkpoint inhibitors. So, there are multiple different guidelines that have been developed. There are even online web applications that can be used to help manage these toxicities. Patients need to continue to be monitored with thyroid function tests, CBCs, liver function tests, while on treatment, every 6 to 12 weeks, but also remembering that unlike the chemotherapy or targeted therapy, when you stop the drug the toxicity appears to go away. These toxicities can occur even after discontinuing therapy and so should be monitored for an additional 6 months post-checkpoint inhibitor. The ACTH and cortisol should be checked in patients presenting with fatigue and also testosterone in men, thinking about pan-hypopit. How often you test should be dependent on the patient. Just because a patient had a test 2 weeks ago and everything was normal, if they present with new onset of symptoms, thinking about imaging or lab work that may help you rule out an immune adverse event is important, and remembering that steroids can reverse almost all toxicities. They're generally reserved for patients presenting with grades 3 or 4 toxicities, or patients with prolonged grade 2 toxicities, as well as infusion-related adverse events. We've seen some patients having infusion-related adverse events at our institution where we have to pre-medicate with steroids before each drug is given.

Dr. Rizvi:

So, we are looking at the autoimmune toxicities. One of the questions which arises, not infrequently, in clinic is what do we do with patients with pre-existing autoimmune conditions, and are they at increased risk for toxicities and how do you approach those situations?

Dr. Horn:

There is some data that's come out, more for melanoma patients, suggesting that those patients are at higher risk for their autoimmune disease flaring, as a result of a treatment with a checkpoint inhibitor. I have not treated a patient who has severe colitis or lupus with a checkpoint inhibitor, but I have treated some patients who have rheumatoid arthritis or psoriatic arthritis with a checkpoint inhibitor. I've always contacted their rheumatologist ahead of time to ask them if they thought it would be safe to proceed. I've made sure that those patients are not on agents such as Enbrel or methotrexate at the time of challenge. And I've had 1 or 2 patients where their rheumatological disease, their autoimmune disease, got a little bit worse, but it seems to be managed by initiating steroids, and it seems to be reversible with steroids. Only because some of the toxicities from colitis and lupus can be potentially more devastating for patients, I haven't used these agents in that group of patients. I don't know if you have at all, Naiyer.

Dr. Rizvi:

No, I think that, as you said, from the melanoma literature, it seems, in particular, the GI toxicities can flare in patients who have ulcerative colitis or Crohn's disease. I think that those patients who are on active therapy would be a relative contraindication. As you know, the trials that we conducted around immune checkpoint inhibitor excluded patients with active autoimmune disease, so it's a bit of a learning curve for us, right now, to figure this out. And I've certainly treated patients who've had psoriasis, and I've also had a couple of

patients with multiple sclerosis who I've treated. In general, it's been manageable. I think that it comes down to the relative benefits versus risks, and when one has advanced-stage lung cancer, I think that one is certainly willing to take more risk, perhaps not in the first-line setting, but certainly in the second- and third-line setting.

Dr. Horn:

Have you ever re-challenged a patient, who had a grade 3-4 toxicity, after their toxicity resolved?

Dr. Rizvi:

I think that the toxicity, where this comes up pretty frequently, is around pneumonitis. I think that we've definitely stopped patients for pneumonitis, and the question is whether we should re-treat them or not? These patients, if they've had a response to immunotherapy, it's not clear whether they need to continue dosing. I don't think we know the duration of these treatments. So, if somebody has a significant autoimmune toxicity, whether it's pneumonitis, or even in some cases other things such as severe skin reaction, if they're responding I tend to observe them at this point, and they may well stay in a state of remission or response even off treatment. If they recur, then I think that it would be worth considering re-treatment for those patients. And my experience, as well as some of the case reports that have been published, would suggest there is a 50-50 chance the toxicity can recur.

Dr. Horn:

So, moving to the second polling question. The following biomarkers have been shown to correlate with response to anti-PD-L1 therapy except: A) Tumor mutational burden, B) Intratumoral T-cell density, C) PD-L1 expression level in the tumor, and D) Intratumoral macrophage density.

So, there has been interesting data with tumor mutation burden, predicting response and potentially progression-free survival, for patients treated with an immune checkpoint inhibitor. There's also been a lot of data with intratumoral T-cell density as well as PD-L1 expression level in the tumor predicting response to anti-PD-1 and anti-PD-L1 therapy, and so the only data that we do not have, as a predictor of response, is intratumoral macrophage density. And I'm going to hand it over to Dr. Rizvi.

Dr. Rizvi:

So, one of the questions that we're going to discuss now is whether there are biomarkers that can predict for response to immune checkpoint inhibitor therapy. Certainly PD-L1 selection is an approved biomarker for non-small cell lung cancer. PD-L1 is not a straightforward biomarker. It has different implications in different tumor types. Within bladder cancer, immune cell scoring seems to be a more reliable predictor of response than tumor cells. Within small cell and mesothelioma, PD-L1 expression does not correlate with response to therapy. But, in general, if you look across tumor types, PD-L1 does predict for response. It's not a perfect biomarker, and there are clearly patients who are negative who respond, and patients who are positive that don't respond. So, it's not binary in nature, unfortunately. Nevertheless, I think it is an effective biomarker, as Leora discussed. PD-L1 positive lung cancer, which is shown, an example of it is on the right, if it's 50% or greater, those patients which represent about a third of non-small cell lung cancer that we see, compared to chemotherapy, if you're that one-third that are PD-L1 50% or greater, the response rate, time to progression, as well as overall survival were improved with pembrolizumab versus chemotherapy. This assay is a straightforward immunohistochemical assay. It can be sent out to a central lab. Many academic centers are also beginning to develop their LDT or laboratory-developed test and performing this in-house as we are doing here. How are you doing the test? Are you doing it in-house or sending it out, Leora?

Dr. Horn:

We're currently sending it out. The problem with the test is, as you know, it's on a DECA-platform and we have Ventana for some of the other tests that are done at Vanderbilt and so, at this time, we are sending PD-L1 testing out. The one thing I was going to say, which I didn't talk about when I was discussing the data, in the first-line, is if a patient's EGFR or ALK positive and is strongly PD-L1 positive, I would recommend using an EGFR or ALK inhibitor over a checkpoint inhibitor, just based on the efficacy and the data that we have. First-line trials have actually excluded that patient population.

Dr. Rizvi:

Absolutely. I think that PD-L1 positivity and EGFR mutation positivity, if you have them both, the mutation status clearly trumps the PD-L1 result. We have a Ventana platform here as well and we've just finished validating, running the Merck 22C3 clone on the Ventana platform and comparing it to the central lab testing, and the concordance is excellent. So, we're basically running the 22C3 assay on the Ventana platform, and other academic centers are doing that as well.

Okay, so, I think PD-L1 selection has become standard of care for newly diagnosed non-small cell lung cancer, both squamous and adenocarcinoma histologies. As we would send patients for EGFR and ALK testing, we would send patients for PD-L1 testing. One of the challenges, however, is that tumor architecture is required. So, typically, this is done off of a core biopsy or a surgical sample. Performing this on cytology or FNA has not been validated, but we and others have looked at that and I think the concordance is good, but we will wait for the data to become more public regarding that.

So, other than PD-L1, I think that the most interest and excitement and data around potential future biomarkers is mutational burden. And when we think about mutational burden, we don't think of EGFR and KRAS mutations, which are oncogenic drivers, but rather the cumulative number of non-synonymous mutations that occur within the tumor. Non-synonymous reflecting a change in the amino acid, so that the immune system recognizes that sequence as different from self. So, the more of these non-self, mutated, protein changes that occur, the more likely there are going to be some that are going to be recognized by the immune system, and these, what we call neoantigens, are likely leading to immune escape, and ultimately immune checkpoint inhibitor therapy restores T-cell response to these neoantigens, leading to tumor regression. And our initial observation is that smokers or ex-smokers with lung cancer responded better than never-smokers with lung cancer is likely related to this differential mutational load and, as you can see from this chart, the patients with the more highly mutated tumors, such as lung cancer and melanoma, are those that respond best to immune checkpoint inhibitor therapy. We explored this in a trial that we published a couple of years back, looking at mutational load by whole exome sequencing of the tumor. And these were patients with pembrolizumab that were treated as part of the KEYNOTE-001 trial, and the analysis of those patients who had durable clinical benefit as partial response or stable disease for at least 6 months of duration, versus those patients that did not have durable benefit, showed that those with higher mutational load had a more likelihood of durable clinical benefit than those with lower mutational burden. And this is reflected in the progression-free survival curve that you see here. So, there's been additional data around atezolizumab as well, showing the mutation load can potentially be a better biomarker than PD-L1. The CheckMate 026 trial, which Leora discussed, was the first-line nivolumab trial where patients were enrolled with more than 1% PD-L1 expression, and the statistical analysis was geared around patients who had more than 5% PD-L1 expression, to see if nivolumab in more than 5% PD-L1-positive patients was superior to chemotherapy. It was not superior to chemotherapy. It was a negative trial. And notably, even the subset of patients who had 50% or greater PD-L1 expression also did not perform better than chemotherapy. And I think there is a lot of confusion around this trial and trying to understand why it was negative, potential imbalances, and so forth, and this, some data, was presented just this week, this last week, at AACR, looking at a tumor mutation burden analysis of the CheckMate 026 trial. And for this trial, there was about 60% of patients had adequate tumor to perform whole exome sequencing, and the tumors were sequenced along with germline sequencing for calling the mutations, and the somatic missense mutations that were detected were used to call the total mutational burden for this trial. And the study was broken into tertiles of patients that had low mutation burden, less than 100 mutations, medium mutational burden, from 100 to 242, as well as high mutation burden, of more than 243 mutations. This is not so different than the threshold that we found in our science paper where we found the optimal sensitivity and specificity in the range of around 200 mutations. So, this is, in a sense, sort of the ballpark of the high mutation burden that you would expect, I think. So, the results were very compelling. For those patients who had high tumor mutation burdens, which was about a third of the patient population on the trial, the progression-free survival was nearly 10 months, and if you had low or intermediate mutational burden, the progression-free survival was 3.6 or 4.2 months. This data suggests that there really isn't a linear relationship between mutations and response, but rather there needs to be a critical level of mutations to generate an immune micro-environment that would lend itself to PD-1 response. And in the chemotherapy-alone arm, what you'd expect is those tumors that were less mutated actually did better than those tumors that were more highly mutated, more mutationally complex, and this has been, sort of borne out in other data sets.

What was also really interesting is the compilation of PD-L1 status and tumor mutation burden was even more robust. So, although the numbers were very small, there were only 16 patients who had both high tumor mutation burden and PD-L1 of more than 50%. You can see the progression-free survival is really remarkable for those patients and they do extremely well. The patients who have high tumor mutation burden and intermediate PD-L1 expressions did better as well, but not quite robustly as both high tumor mutation burden and PD-L1 more than 50. I think what was really interesting is that if you had low or medium tumor mutation burden, even if you had a PD-L1 score of more than 50%, the progression-free survival was actually really disappointing. So, I think that it really supports mutational burden as an important biomarker to predict response to immunotherapy. So, one of the challenges we can't necessarily, certainly today do a whole exome tumor and germline sequencing on everyone that we see because of the logistics and time to obtain a whole exome result which is still a little on the long side, but in this study, as well as in other analyses that have been performed with atezolizumab, for example, the correlation between exome mutations versus the genes just in the FoundationOne panel, the correlation was extremely tight. So, basically, what they did was they counted the number of mutations that one would detect on the 315 genes in FoundationOne's panel, and see how that correlated with the total exonic mutations, and the correlation was very tight. So, conceivably, you could make that assessment on a FoundationOne panel. And, actually, you do, even today already, you can get a mutational burden score on your Foundation Medicine report. When you get the total mutations that are present, it will also be scored based on the total mutational count as intermediate, low, or high mutation burden.

Dr. Horn:

So, Naiyer, I have a lot of community doctors who are asking me about this data, because most community centers are doing EGFR, ALK, ROS-1 and PD-L1 and they're not necessarily sending off to places like Foundation Medicine, primarily because insurance often won't cover the cost of NGS. So, is this something that people should be thinking about in helping them select therapy, or should we

wait for more data before we make any decisions based on these data that's emerging?

Dr. Rizvi:

I think we need more data before we make treatment decisions based on mutational burden analysis. It's hard not to imagine that there are going to be perspective trials looking at mutational burden as a predictor of response, and I think that trying to determine what the optimal threshold is, how PD-L1 and mutational burden together could represent a composite score. So, I think that it's definitely quite robust. It probably can help you more in other tumor types than lung cancer, where these drugs may not be as approved, or where the response rates are more variable. I think, for lung cancer, everyone's going to get a PD-1 therapy at some point, either first-line, second-line, or third-line, so they're going to get it anyways. Right now, I think we need to wait on some more perspective analysis before we use mutational burden, but I think it's a useful result when you see it, but I don't think we should be mandating it. Is that your experience?

Dr. Horn:

Yes. I agree.

Dr. Rizvi:

I think that to your point, whether we should be using this as standard of care, in our analysis that we did, trying to understand why some of these patients who had highly mutated tumors, they didn't respond. And we had a few patients who had 3, 4, 600 mutations who did not respond to immune checkpoint inhibitor therapy, and in collaboration with Charlie Swanson, who performed a clonality analysis of our patients that we treated with pembrolizumab, and had whole exome sequencing data on the left, you can see, patients represent the responders to immune checkpoint inhibitor therapy and in the blue represents those patients who have very clonal mutations, clonal neoantigens, and you can see the responders on the left are those that have tumors that are very clonal in nature. And they, in general, have high PD-L1 levels, in the bottom squares, mostly in the red range, or pink, and very few negatives. So, there does seem to be some relationship between PD-L1 expression as well as tumor mutation burden, but the clonal nature of the mutations; whereas, on the right, those 3 patients in arrows, who had a lot of mutations, but did not have a response to immune checkpoint inhibitor therapy, actually had a significant subclonal fraction, suggesting they're very heterogenous tumors. And so, I think, we still have a lot to learn regarding the nature of the mutational landscape that could predict response to these therapies.

So, in closing, I'd just like to summarize and say that we've made some great progress with immune checkpoint inhibitor therapy in lung cancer, and I think that there's definitely going to be more to come. I'm Naiyer Rizvi from Columbia University. Thank you for participating in this activity.

Dr. Horn:

I'm Leora Horn from Vanderbilt-Ingram Cancer Center. Thank you for joining us.

Narrator:

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