**Gary Shelton (Moderator):** ...back, everyone. I'm pleased to welcome back Beth. And introduce our next speaker, Dr. Marianne Davies. We could talk a lot about Marianne and myself, but we won't, okay. Marianne is a Nurse Practitioner at Smilow Cancer Hospital at the Yale New Haven Health and is Associate Professor at Yale School of Nursing. Marianne will be discussing, along with Beth, the role of immune checkpoint inhibitors with and without combination therapy for nonmutated metastatic non-small cell lung cancer, followed by the management of immune related adverse events. Which, obviously, we want to keep our patients on our treatments, right? So, symptom burden, we should all be right there doing our best. Marianne?

**Marianne Davies:** Thank you, Gary. And thank you to Beth and for JADPRO for having me here today. I'm very excited to be talking about immunotherapy, I'm very passionate about it. Gary and I have known each other for many, many, many, many, many, many, many years, so that's just, we've done a lot of presentations together. As have Beth and I. So, today we are going to be talking ... I'm really like height-limited, so I'll be careful about where I stand. We're going to be talking about approvals for immunotherapy. And in case, I forget to mention it as we go along later on, you have the ability on your iPad to actually touch and zoom in on certain images, which might make it helpful to see, because there's a few slides that are rather data dense or contact dense, and also there's some imaging that might be a little bit more difficult for you to see on the slide itself. So, we're going to get right in. So you know who the ... You've seen these slides already as far as our disclosures and our speakers.

So our learning objectives today are really to look at efficacy and safety data, and really that supports the use of these targeted therapies, specifically immune checkpoint inhibitors in treating non-small cell lung cancer. So, as Beth mentioned earlier, we are going to have a separate section on small cell lung cancer. So the data I'm going to be talking about, again, is nonmutated, non-small cell lung cancer specifically for today. Again, we'll review the role of chemotherapy in the metastatic setting. And we'll also talk about how really treatment scheme has really changed in the past five years, specifically in the first-line setting with and without chemotherapy and the use of immune checkpoint inhibitors. And then also the role of immune checkpoint inhibitors for second-line treatment. And then begin a discussion about what we do for patients in the second-line and beyond. Fortunately, we actually have an opportunity to have that discussion now. Whereas, as you saw by the other data, we didn't have that opportunity, the patients weren't living long enough really to get to those other lines of therapy. So it's really, the dialogue will continue.

So we're going to start with a question. Did you want to read the question?

**Beth Eaby-Sandy:** Sure, yeah. I'll read the question. So it's a 68-year-old male who presents with metastatic non-small cell lung cancer with adenocarcinoma histology. He is fit, has a good performance status, and is ready to start first-line treatment. He would like to learn more about which treatment offers the longest survival. Based on this goal, which treatment would you offer as best position to meet his goal? Is it, one, pemetrexed, carboplatin, and nivolumab? Two, pemetrexed, carboplatin, pembrolizumab? Three, a taxane plus carboplatin, bevacizumab, and atezolizumab? Four, is it taxane, carboplatin, pembrolizumab? Or are you unsure?

**Marianne Davies:** All right, so then we'll move on.

**Beth Eaby-Sandy:** There should be another question. Yep. The five year survival rate for patients with metastatic non-small cell lung cancer who had a PD-L1 score of 50% or greater and were treated with single-agent first-line pembrolizumab was approximately: 5%, 10%, 20%, 30%, or you're unsure.

**Marianne Davies:** I always get the old lady music that plays during my sessions. You know, Gary, didn't I mention this at last presentation. I know. They look at me and say, "Okay, old lady. This is ..."

**Beth Eaby-Sandy:** You're not getting Metallica right now.

**Marianne Davies:** I know. I don't know what it is. All right, so unsure. So we've got some work to be doing in this session. You've seen this slide before in terms of the spectrum of what we see for lung cancer stages. And this is really historic SEER data. So, we're specifically going to be speaking about patients today that have distant metastasized, so this makes up 57% of the patients at new diagnosis. Clearly, we're not going to get into this discussion today, but we have a long way to go as far as moving up that trajectory, as far as early diagnosis for lung cancer patients, so that we can begin to change this slide in the future.

As has been mentioned before, the first step in how we approach our patients with disease is really going to be looking at their histology, as Beth mentioned before and others. The pathology is really key to help begin our direction for our patients. If we look at breaking down that pie chart, the 57% of the patients that are diagnosed with metastatic disease within the context of that, we've got really the largest percentage is going to be patients that have an adenocarcinoma histology. And that makes up 55%. And when we look at the other portion, it's the squamous cell, and that makes up 34%. And then there is the subset of patients, about 11% of patients, that have a mixed histology. So it may be a variant of large cell, it may adenosquamous combination. And there are fewer patients also that have a mixed histology with an adeno with even some small-cell features too. We're not going to address those today. They become a little bit more complex as far as management.

We'll start with those patients that have a predominance of adenocarcinoma, and begin to look at the data for these patients. We're going to start with a case study. Mrs. Adeno, I'm sure you really appreciate that name, is a 69-year-old, comes to you for a treatment consideration for a stage IV non-small cell lung cancer, again, adenocarcinoma histology. She smoked for 45 years, so keep that in mind. Having just quit about six months ago, when she started having some symptoms. So she had started to have some fatigue, shortness of breath, a cough, and associated weight loss. Which sounds like all of our patients that walk into our clinic. Keep in mind, she's got a good performance status when she first comes to see you.

Long story short, she has scans, x-rays and scans, which identify that she has a likely lung malignancy. And has a biopsy, which demonstrates on her DNA sequencing that ... Actually, the DNA sequencing was sent off and so that's still pending at this particular time. Her PD-L1 testing came back and FISH, which were done internally, so those results came back pretty quickly. So she's got a PD-L1 expression of 65% and FISH or IHC negative for ROS1 and ALK. So those are the only mutations that we have so far on this particular patient.

So given that, let's go back and just take a step back and take a look at the first chemotherapy. So historically, for the past ten years, chemotherapy has really been in our treatment scheme for all of these patients that have metastatic disease. And really the foundation, the core initial therapy that really gives us the most bang for our buck has either been the cisplatin and carboplatin. So, that's really been the anchor of how we've treated patients with this disease. And then the NCCN has really supported the approval of any of the other drugs that are listed below, so docetaxel, etoposide, gemcitabine, nab-paclitaxel, and vinorelbine. When we look at all of those combinations, over the past five years, what has really stood out and been superior as far as outcomes, has been the pemetrexed

combination with the platinum-based regimen and been demonstrated to be more superior to gemcitabine. And not only superior, but also with a lower toxicity profile. So that's really been our foundation for how we've approached if we were going to use just a chemotherapy regimen.

We also have a consideration as to whether or not a patient is a candidate for an additional agent, so not just using two agents, but using a third to see if that would enhance outcomes. So bevacizumab, as a monoclonal antibody, angiogenic agent, is also approved in combination in eligible patients. We can talk about those, what meets eligibility requirements. Bevacizumab is approved in the nonsquamous histology population, those that are not at risk for hemoptysis or have other eligibility criteria. So those are our options. That's really what we've relied on for the past ten years, as far as our treatment recommendations.

With the advent of immunotherapy, my favorite thing to talk about, we now have many other options to really consider for patients. One of the first ones to be approved for immune checkpoint inhibition was nivolumab. It is approved in metastatic non-small cell lung cancer after failure on a platinum-based chemotherapy regimen. And this approval is independent of PD-L1 status. And we'll mention this a few times, because for those of you that work in clinics where you might treat a variety of different malignancies, you'll see that there are just a few diagnoses where there's a call out that you need to assess that PD-L1 status. It's not across the board. So for instance, in melanoma you don't need to asses PD-L1 status, but some other diseases you do. And so, the analyses that are used are either the PD-L1 expression, and that might either be a tumor proportion score or a total combination score. So there's some subtleties as far as how that's reported on your molecular profiling. We'll focus just on non-small cell lung cancer for today.

For nivolumab, again, it's second-line setting. It is a PD-L1 inhibitor. And the initial approval was for dosing it every two weeks at 240 milligrams IV every two weeks. Then had recent update where this can be administered at 480 milligrams every four weeks. And so the decision really is going to be based on that patient specifically. What is the patient preference? Where is their location? How closely do you want to monitor that patient? So that really is provider specific, as far as that dosing scheme-

**Beth Eaby-Sandy:** Marianne, have you had anyone that was on the 480 every four weeks that seemed to have more toxicity than on the every two week dosing?

**Marianne Davies:** I would say yes. Not across the board, not every single patient. But there is a subset of patients that did, had a high, at least ... This, again, is subjective. I don't have any research data to prove this. But I would say subjectively had either more arthralgias, or more fatigue, or more of the lower grade immune toxicities.

**Beth Eaby-Sandy:** Yeah, I had one in particular as well, though I can't say it's across the board, because I've had other do the q four week okay. But I did have one in particular that seemed to have more toxicity. And he had been on the q two weeks. And then when it got approved he was like, "Woohoo! I only have to come once a month." And then he had more toxicity, so we reverted back to the q two week dosing.

**Marianne Davies:** So I would say, so every once in a while, when we're short staffed, I have to cover in the melanoma clinic, so we saw the same thing in the melanoma clinic. If patients started at 480, they tended to have lower toxicities than the patients that started at 240 and then went to the 480. So that,

again, that's just anecdotal. But you certainly can go back to every two weeks. And I would say another thing that I take into consideration is how closely do I want to monitor that patient? What is their tumor burden? And do I want them coming in every two weeks? So, that may be factored into how you make your decision about the scheduling.

Again, our patient is first-line, so we'll go into pembrolizumab is the next agent that was approved in metastatic non-small cell lung cancer. In the pembrolizumab package insert, and it's FDA approval, we do need to take into consideration PD-L1 expression, tumor proportion score. So it's approved in the first-line as a single-agent for patients that have a score of greater than 1%. So initially it was 50%, but now it's been updated to say 1%. It's also approved in the first-line setting now in combination with the platinum-based regimen and that's independent of PD-L1 status. Let's say you don't know what a patient's PD-L1, you don't get enough tissue or they have a low expression, this might be an option. So first-line. So those are the two first-line indications. It's also approved in the second-line after failure of a platinum-based regimen, and that's, again, if your TPS score is greater than or equal to 1%. And again, as you heard previously, for those that are locally advanced with a TPS score greater than 1% if they're not a candidate or refused concurrent chemo/rads. Again, pembrolizumab is a PD-L1 inhibitor and it's dosed at 200 milligrams IV every three weeks now.

The third for the first-line that we're talking about is going to be atezolizumab and that's metastatic non-small cell lung cancer. It's approved second-line after failure of a platinum-based regimen, independent of PD-L1 status. Or approved in the first-line setting in nonsquamous, again in combination with a taxane base plus carboplatin with the addition of the bevacizumab. So in this case, you need to consider whether a patient is a candidate for that bevacizumab. Atezolizumab is a PD-L1 inhibitor, and really interesting dosing regimens. So I think based on your institution, you may have different experiences with the dosing. It's either 1,200 milligrams IV every 3 weeks. And then in maintenance or as a single-agent, you can give it at 840 milligrams every 2 weeks, 1,200 milligrams every three weeks, or 1,680 every four weeks. I've never given the four week dosing. Have you, for this?

**Beth Eaby-Sandy:** I've stuck to the three week if we're going to do it.

**Marianne Davies:** Right, yeah. So, that's basically what we've done in our organization too. But know that that is an option for your patients. Obviously, you wouldn't do the four week dosing if they're getting it in combination with the chemotherapy, because that's going to drive the every three week dosing for that patient.

All right, so we're going to go back to our patient now. So, Mrs. Adeno, 69-year-old adenocarcinoma. She has high PD-L1 expression, ALK/ROS1 are negative. So how would you manage this patient?

**Beth Eaby-Sandy:** Well, would you wait for her molecular to start treatment?

**Marianne Davies:** So, I'm just going to say when you go back to the patient's history, she's a heavy smoker. So really consider do you really think this person is likely to have an EGFR mutation. That would be the first thing I would think about. I think probably unlikely given the fact that she's 69 years old, heavy prior smoking. Is it possible? It's possible that she has a mutation, but unlikely.

**Beth Eaby-Sandy:** BRAF?

**Marianne Davies:** Well, maybe. Again, much smaller percentage of the patients. So, I guess the other thing that I would consider, aside from the molecular testing, is, in terms of managing this patient, really what is their disease burden. Can I afford the luxury of giving them an immune checkpoint therapy, which might take longer time to response? Or do I feel that they need the benefit of the chemotherapy, where you're going to have more rapid response to therapy. So I think those are the key things that I use as far as in my decision making. How about you?

**Beth Eaby-Sandy:** I think, I agree with you. I think she has a low likelihood of having a ... And truthfully, we can say, we already know ALK and ROS1 are negatives, so it's unlikely she has EGFR, BRAF though she could. And those are targetable first-line. But it's unlikely. In a perfect world, I'd like to have it back. But in this case, I'm probably don't want to wait too much longer. Am I going to hound my molecular lab? And what if they say it'll be two more weeks. Well, do I really want to wait now two more weeks as a patient with metastatic lung cancer? These cancers are on the move, they're quick. I guarantee she doesn't want to wait. This is the waiting game that we play with patients with these molecular path reports. I think, personally, it would be reasonable to start her systemic therapy and assume those are negative, but that's not probably the right answer. Probably the right answer would be to wait, but you have to manage that in. Tyler, your thoughts?

**Tyler Beardslee:** Yeah, so there's drug interaction over in my talk that I just want to mention right now. There was some data, I think it was out of Sloan, that came out that showed that patients that have immunotherapy and then they go EGFR inhibitor with osimertinib, they have an extremely high rate of pneumonitis. So if you don't have the EGFR result here, and you think there's a possibility if it coming back positive, you might, and you want to start treatment to get some type of response, you might not want to do immunotherapy. Because like I said, if you go immunotherapy and then osimertinib, there's a very very high rate of pneumonitis.

**Beth Eaby-Sandy:** Yeah, Rasheda and I are going to touch on that in the EGFR talk, but you are absolutely right. I think for this patient who I don't suspect it, I would be okay with starting it. But you're absolutely right. If you start chemoimmunotherapy and then they have an EGFR mutation, the drug of choice, which we'll get to, will be osimertinib and giving that right after immunotherapy has a particularly high rate of pneumonitis. Much higher than the average patient.

**Rasheda Persinger:** And Marianne, at your institution, are you all, from an insurance standpoint, because at our institution if we don't have those molecular results back, regardless if our clinical picture says that more than likely they won't have it, we're not getting approval for immunotherapy. We're able to go to systemic therapy and have to add in the immunotherapy. So I was just curious-

**Marianne Davies:** I would say, it's not our institution, it is the patient's insurance that really has driven this. And most of their insurances are approving the immunotherapy upfront without the testing. But there are a few, there are a few that will request it. And exactly to your point, we will start the chemotherapy initially, and then with cycle number two, add the immunotherapy in, once we get that. And in terms of the other point too, I think in talking about sequencing, that really is becoming the biggest challenge for us in how we're sequencing therapies for patients and looking at those particular toxicities. And we'll talk a little bit later on about a positive outcome of starting immunotherapy earlier before going to some other chemotherapy. Again, those are really the challenges.

Another challenge now for this patient, so this patient-

**Beth Eaby-Sandy:** Wait, I have another question for you. Would you do single-agent immunotherapy or would you do chemotherapy plus immunotherapy in this patient with a PD-L1 of 65%?

**Marianne Davies:** So, in general, again, I don't have her scans. I don't know what her disease burden is. If the patient had really big, bulky disease and there was a risk of, let's say, pulmonary collapse or whatever, if they had a lot of bulky disease then I would start both. If they didn't, if they had just an isolated area of metastatic disease and a lower disease burden, then I think for this person I would go single-agent, would be the recommendation.

**Beth Eaby-Sandy:** And what if it was a PD-L1 of 10%?

**Marianne Davies:** If it was a PD-L1 of 10%, I think I would definitely still go with the dual chemotherapy for that patient.

**Beth Eaby-Sandy:** Yeah, so I'd like to just talk about that briefly, because initially when pembrolizumab received its approval in the first-line was 50% or higher as single-agent. And we're going to show that study in just a second here. But then they expanded the indication to be 1% or higher, but I think a lot of us, the physicians I work with don't feel comfortable with just single-agent immunotherapy for those low expressors. I think the high expressors, we feel pretty confident, but there's still somewhat of a lack of confidence. So, even though it's approved in that setting, we're often between 1% and 50% still using the combination of chemoimmunotherapy.

**Marianne Davies:** It's still that gray area-

**Beth Eaby-Sandy:** It is but I think it's-

**Marianne Davies:** It's your comfort level too, I think.

**Beth Eaby-Sandy:** ... a little gray.

**Marianne Davies:** So the next challenge we have now for this patient is that she does have another medical condition in terms of rheumatoid arthritis, on weekly methotrexate and hydroxychloroquine and also 10 milligrams of prednisone. Based on all the clinical trials, the clinical trials really didn't, they excluded patients that had coexisting autoimmune diseases, so initially we didn't have a lot of data. And we began to collect the data after the approvals went through, certainly in the melanoma population. So there's a lot of prospective studies now that are actually going on, looking at enrolling these high risk patients that have autoimmune diseases.

For this patient, I would say, I would take this into considerations, certainly work with their rheumatologist in terms of seeing if we could taper off of some of the immunosuppressant agents. But for one of the things, we need to consider is that there is a risk of exacerbation or worsening, certainly, of their underlying autoimmune disease. And what's really key for that patient is, one, are they going ... The questions I would ask, and this all has to go to your shared decision making with your patient, is there a risk of them dying of their lung cancer? And can they live with an exacerbation of their rheumatoid arthritis? Those are the subtle, not so subtle, conversations you need to have with your patient is how do I make that decision. That will come into play. It's not in the package insert for any of these as an exclusion, so you certainly have an option of using an immune checkpoint inhibitor, but just

know that there is that risk, and you've got to be very straightforward with your patients about evaluating that risk.

**Beth Eaby-Sandy:** This was a real patient of mine and we ended up working with the rheumatologist and we stopped the methotrexate, because we felt like that was too immunosuppressive and would counteract. But we allowed her to stay on the hydroxychloroquine and the prednisone. We allowed the prednisone 10 milligrams. Your thoughts on that?

**Marianne Davies:** Well, there's been actually several studies that have looked at dosing of prednisone. And, in general, kind of across the studies, and this is across the diseases as well, for patients, if you can, even if they've developed an immune-mediated adverse event and they have to start on steroids, if you get them tapered down to a dosing of ten milligrams per day, then there's no detrimental effect or impact on the immune checkpoint therapy. In general, our rule is if we can get them down to ten milligrams and keep them there and maybe get them off, that would be great, but at least get them down to ten then we are absolutely comfortable and know that there's no negative impact on the outcomes. For this person, I wouldn't be that worried that they're on ten milligrams of prednisone. I would feel comfortable certainly eliminating the methotrexate and then proceeding.

**Beth Eaby-Sandy:** Okay, thanks.

**Marianne Davies:** All right. So now let's take a look at some of the data that actually led to the first-line approval. So the KEYNOTE-024 was a randomized, multi-center study really looking at can we improve upon a standard of care. There were 305 patients. They were previously untreated and these patients specifically did not have an actionable mutation, as we were talking. They don't have an EGFR mutation, they don't have an ALK mutation. And this is a subset of patients that were on this study, specifically looking at patients that had greater than 50% expression, PD-L1 expression. And so, they were randomized to receive, a one-to-one randomization to receive pembrolizumab at 200 milligrams per kilogram every three weeks for 35 cycles, so over a few years. Or the investigators choice of a platinum-based regimen every three weeks. Then the primary endpoints were progression free survival, with secondary endpoints of overall survival, objective response rates, and safety.

And just like a little aside, when we look at this advanced non-small cell lung cancer, almost 30% of these patients have high levels of PD-L1 expression. So, that's really something that we need to keep in mind. And that's specifically when we're looking at the tumor cells. So, that means it's more than 50% the tumor cells that have that expression. Okay? That we need to take into consideration.

You can see, I think it's [inaudible] was very dramatic in terms of favor in pembrolizumab on this patient. When we're looking at this, this is out 18 months. I want to just go back to the very first slide that really looked at our five year survival rates, which was less than 2% of patients historically, and how we're beginning to think about how we're going to shift that curve. It's the first single-agent immunotherapy that really outperformed a platinum-based chemotherapy regimen. In general, less toxicity than a chemotherapy based regimen. It was because of the striking results of this study that led to the approval of this as a first-line therapy. When we look at ... I'm sorry, if I go back, it was progression free survival and then also looking at overall survival. I think the interesting thing to look at is really how this plateaus off and how these patients continue to have sustained responses. So, really the first time we've historically seen that in the metastatic setting. So, this was just a couple of years ago that this result led to that approval.

Fortunately, there was a look at the five year overall survival as a result of the KEYNOTE-001. Now this is a different study, but really was based on single-agent therapy with pembrolizumab across multiple tumor types. When you looked at that subset, that cohort of non-small cell lung cancer patients that got treated, and there were 101 that were treatment naive that were treated on multiple studies, the median overall survival was 22.3 months for single-agent pembrolizumab. Really just fascinating. Things that we just never saw with chemotherapy before.

**Beth Eaby-Sandy:** You should all be falling off your chairs. This was really exciting.

**Marianne Davies:** This is what we're trying to move, this five year relative survival rate. So we're going to really need some long-term data. But we're beginning to see it now, that this bar is going to be changing. Again, overall survival for five years, 23.2% of patients that had any level of PD-L1 expression and almost 30% for patients that had greater than 50%. I mean, that is just, I don't know ... I've been working with lung cancer for 25 years now and this is just absolutely amazing.

**Beth Eaby-Sandy:** This was completely mind blowing to me. So, I've been in lung cancer for 16 years and I was taught, initially, we don't talk about five year survival rates in metastatic lung cancer. I mean, 5% actually bigger, when I started it was 1.9% and then it got in the twos for a while. Now since immunotherapy, it's gone up to around 5%. But even 5%, that means 95% of your patients aren't around at 5 years.

So, I was kind of always taught that when patients came in and said, "Well, I really want to see my son graduate high school in five or six years," obviously, I didn't sit there as a provider and say, "Well, that's not going to happen." But we would often steer them in ... Gary could probably speak to this a little bit better on how you manage expectations of patients in a way that doesn't kill their hope. But oftentimes we would say, "I hope for that, but unfortunately, the survivals aren't there." However, now 30% of patients with that subset of 50% or higher on average were alive. That's incredible. I've rethought my entire thought process now, because now I wouldn't say that it's necessarily unlikely. Again, it's still, obviously, 70% aren't, but it's just completely different. It's not unheard of at this point. It was unheard of 10, 15 years ago.

**Marianne Davies:** You could never use the word cure before, and now we're beginning to dip our toe in that a little bit for a certain subset of patients.

**Beth Eaby-Sandy:** Well, and that's not a cure, but it's just means they're living, they're just living long. My goodness, they could live five, seven, even ten years with metastatic lung cancer. That was just never, ever something 10, 15 years ago that really ever happened outside of miracle cases of 1% to 2% of patients.

**Marianne Davies:** So, hopefully, in ten years when we come back, this graph will be completely flipped.

**Beth Eaby-Sandy:** Yeah, it's really exciting. I think, hopefully, we can better analyze what did those 30% of patients have in common and how do we pull those out and figure out ... Or those 23% that even lived that long with other PD-L1 expression levels, is who are they? What was it about your case? So hopefully we're going to learn that.

**Marianne Davies:** More personalized therapy-

**Beth Eaby-Sandy:** This is my most exciting slide. I made this over the weekend in Barcelona at the World Lung Conference. I'm like, "Look! Isn't this amazing?"

**Marianne Davies:** We're still suffering from jet lag.

**Beth Eaby-Sandy:** I know. It's very exciting.

**Marianne Davies:** World Lung is really exciting. All right. I'm going to move on, because I know in the interest of time. We talked about patients that have high expression, how exciting that is. So what do we do for the other people that have any level of expression? So we've got some additional data to really take a look at that. The KEYNOTE-189 study was a combination of chemo, pembrolizumab or the chemotherapy alone. So very similar. So metastatic nonsquamous non-small cell lung cancer, no activating mutations of EGFR and ALK. Those were specifically written into those trials several years ago when they were developed, because we really didn't understand the significance of some of the other mutations. But, essentially, anybody who didn't have a driver mutation could be on this for first-line. They had no prior systemic therapy for metastatic disease. And randomized. The pembro every three weeks with combination of the pemetrexed, carbo, or cisplatin versus the pemetrexed ... Again, the pemetrexed therapy was allowed on both. And they were looking at overall survival, progression free survival for these patients.

When you looked at the results, at 12 months, 69% of the patients were alive at 12 months, when we look up here. Which is really fascinating as well. Versus 49% of the patients that were on this placebo-controlled arm. At the time that this was first published, this was actually, this is just in 2018, initially, the median overall survival was not yet reached in this population. But very clearly striking scale to really demonstrate that there was benefit for the pembrolizumab. And I think the other, the median overall survival was updated at ASCO. Again, this is kind of just earth shattering as far as us. But the median overall survival for both arms was finally reached. And it was 22 months in the patients that had the chemo and IO combination versus ten. So really doubled the overall survival for this patient population.

The other really interesting part, and this really goes to the point of sequencing of our therapies that I just want to highlight, is that, if we looked at patients that went on to get further treatment beyond that treatment, so that was then that follow-up, the patients that had been on the pembrolizumab arm, even though they might have had subsequent treatment, they had still a progression free survival longer than those that did not have the benefit of the checkpoint therapy in that first-line setting. So, that's very very fascinating. Again, keeping in mind thinking about that sequencing for your patients.

**Beth Eaby-Sandy:** And I think that just goes to show that even after they stopped the pembrolizumab, whatever they got in the second-line, docetaxel, whatever it was, they were probably still getting benefit from that immunotherapy even after it was stopped. So, that was such an interesting statistic out of that abstract.

**Marianne Davies:** You know, there's some thoughts that there's just that priming of the immune system. That even if you're getting other therapy after, those patients are going to benefit. So, again, that should factor in when you're making that decision.

**Beth Eaby-Sandy:** Or get toxicity.

**Marianne Davies:** Right. In oncology, what do we do? You try one drug, you try two, you try three, and know if four going to be better. So the next question.

**Beth Eaby-Sandy:** Why not?

**Marianne Davies:** So the IMpower150 study really looked at that particular question. So again, stage IV non-small cell lung cancer, nonsquamous histology, chemo naive. And the patients could have had any level of PD-L1 expression, but it was taken into consideration in terms of the randomization to assure that all of the arms of this study, all three arms, had equal representation from PD-L1 expression. In addition, the stratification included looking at gender, and also whether or not the patients had liver metastasis, because there is some thought that liver metastasis and possibly impact on hepatic function my influence those outcomes.

So the first arm, Arm A, was the atezolizumab, carbo, and paclitaxel for four to six cycles, followed by maintenance atezolizumab alone. Arm B, which is really the experimental arm here, the question was really looking at the atezolizumab, carbo, paclitaxel, and bevacizumab. So again, four to six cycles of this. And then going on to maintenance atezolizumab and bevacizumab. And then the control arm was the carbo, paclitaxel, and bevacizumab for four to six cycles with bev as maintenance therapy, and looking at outcomes for this patient population.

**Beth Eaby-Sandy:** I love that you can say all of those words so well.

**Marianne Davies:** It's taken a long time. In this combing, the combination to the four drug regimen, so the atezo, taxol, platinum-based regimen, and the bev did show superior progression free survival. So 18.3 months versus 6.8 over the-

**Beth Eaby-Sandy:** Eight point three.

**Marianne Davies:** Oh sorry. It's 8.3, versus the other. And the median overall survival was also improved from 14.7 to 19.2. Some of the things to take into consideration is does it make sense to use this regimen. You've got to really make sure you're doing an appropriate assessment for that patient. I would say, Beth, for you, how would you make that decision as to whether or not a patient got this four drug-

**Beth Eaby-Sandy:** So I think the big question here is, in this nonsquamous setting, would you pemetrexed, carbo, and pembrolizumab, or would you use this four drug regimen? And does that create a benefit? And you can actually go on to the next slide, because the next slide actually, I think I did ... Yeah, I did like a little graph of the different ... If you look at them, again, these are not head-to-head, but if you look at the median overall survival in PFS in the different regimens. So they're somewhat close. You can see the pem, carbo, platinum, and pembrolizumab is 22 months versus 19 months for the four drug regimen. So they're very close in overall survival, but do you want to risk the toxicity of four drugs versus three? It's just very interesting what regimen is correct to use. Obviously, the bevacizumab could add potential cardiac toxicities, though in relatively a safe drug that we've used over the years.

If you go back now to the back slide, I put in there a specific population where we have used the four drug regimen.

**Marianne Davies:** It's not going back. Can you put us back to the previous slide? It's not ... Oh, there we go, there we go.

**Beth Eaby-Sandy:** So the one area that we have considered using that four drug regimen is in the patients who do have mutations. So, say an EGFR mutated, an ALK patient, who has exhausted all of their front-line therapies. So, they've had EGFR inhibition, they've had second-line EGFR inhibitors, or ALK inhibitors for two, three lines. They've exhausted clinical trials. Now where are we? Well, we're back to good old chemotherapy with you. But we know that immunotherapy doesn't work great in those settings, so-

**Marianne Davies:** Patients can still have responses, but the data is not there to support that it is. Not as strong.

**Beth Eaby-Sandy:** It's not as strong in favor. So the thought is, "Well, if we add all four ..." Now there's no data to support any of this, but the thought is that maybe the four drug regimen hitting them from an immunotherapy, a VEGF standpoint, and chemotherapy might be, I don't know, a way to induce more of an immunotherapy side effect. There's absolutely no data for that, but that is one place we have used it. I can say traditionally, my run of the mill, stage IV adenocarcinoma lung cancer patient comes in, we're more likely to use the three drugs, the pemetrexed, carboplatin, pembrolizumab over the four drug regimen due to risk of toxicity, not superior when you extrapolate the studies out, there's no head-to-head. Financial toxicity, again, this is four drugs, two of which are monoclonals that are expensive to ... I think there's two different regimens that could be used in that setting, in especially the low PD-L1 setting. Your thoughts? Have you ever used the four drug regimen?

**Marianne Davies:** Absolutely, and it's in exactly that setting. It's those patients that do have actionable mutations that have exhausted, because you're just trying to enhance the potential for them to respond to that combination therapy.

All right. We're going to now go on. We've already gone over this. So now, we're going to switch to squamous. So we know that this histology makes up about 34% of our patient population. And so now we've got Mr. Squam, must be an interesting ... Very creative.

**Beth Eaby-Sandy:** Barcelona, my head was not ... There was no more creation that was going on at that point.

**Marianne Davies:** Oh my goodness. So 72-year-old gentleman with metastatic squamous non-small cell lung cancer. PD-L1 expression is 0. Two pack per day smoker, even though he cut back. He does have bone mets, which was radiated. So just keep that in mind. He has shortness of breath at baseline and significant weight loss. Also, diabetic. So I just want you to tuck that away for future reference.

So, really the same concept as our adeno population. I mean, platinum-based chemotherapy has been our platform for so many years up until really recently with immunotherapy, with immune checkpoint inhibitor, with just the caveats, the patients that squam histology are not eligible to receive pemetrexed and bevacizumab. So I think that's just been our foundation that we're certainly all well in

tuned with. The NCCN does endorse multiple different treatment regimens. Really the selection is going to be based on that toxicity profile, comfort-level in your organization, and in some organizations it's going to be based on your pharmacy, what they have in their formulary for what they're going to approve, if you've got institutional guidelines in terms of driving best practice. We right now are participating in that ... Oh, I can't even remember the name of the organization now. Maybe somebody can shout it out. What is that-

**Beth Eaby-Sandy:** Like a pathway or-

**Marianne Davies:** Is that ... Yeah, Via pathways. Is anybody else here using Via pathways? Okay. So Via pathways is really what prioritizes the regimen for us, so it really kind of takes out the decision making for us. Those are all approved.

So, now let's take a look at exploring the use of immunotherapy in the squam populations. So the KEYNOTE-407 really strove to answer this question. So untreated patients, stage IV. There was some assessment of their PD-L1 expression, though not an exclusionary criteria. Patients were not to have any symptomatic brain metastasis and no history of pneumonitis on their scans. Again, stratification based on PD-L1 expression, the choice of the taxane that was used, and also geographic region, whether it was East Asia or the rest of the world. And as was alluded to in the earlier discussion, we do know that histology and even your molecular profiling may not be all of the characteristics that we need to look at, but there's certainly some genetic factors that come into play in terms of responses to different therapy. Whereas, Asians respond very differently. And these are patients that continue to reside in those regions of the world, versus patients of the rest of the world. Be looking for those kind of things factored into the clinical trials as we move on.

The two arms, pembrolizumab, carbo, taxel or nab-paclitaxel for four cycles followed by pembrolizumab every three weeks as maintenance or the placebo-controlled arm. And those patients were followed for progression free survival and overall survival as the primary endpoints. Just a little caveat for this that there was the ability if the patient started to have some progression of the disease and they were unblind and on a placebo, there was ability to cross over and have those patients go onto the pembrolizumab as a factor in this clinical trial.

And this is just, I really find this so fascinating. So when they broke out, remember these patients were fairly balanced between the two arms, all three arms really did demonstrate the benefit of the addition of the immune checkpoint therapy. Patients that had a TPS total proportion score greater than 50% had the best benefit and was seen earlier on, and when we look at the far right hand graph. But those patients that had even the 1% to 49%, it took a little bit longer, it took up to several months, a few scans that were really kind of head-to-head, but then eventually those patients really did demonstrate also an improved progression free survival. And again, took a little bit longer for those that has less than 1% or 0% expression. It was really fairly well balance up until about the nine month or six month mark, and then those patients that were on the full combination actually began to demonstrate on their scans their benefit.

So really, do we use it in squamous cell? Well, it's a consideration. It provides an opportunity for you to say, "How can I enrich for best benefit for this patient? Who's really going to ... Who can I speculate is going to do better?" And so you know those patients who have a 50% one are obviously going to do better than those that have lower, but don't exclude it as far as one of your treatment options, because you can still get benefit for those patients.

When we look at overall survival, you can see that that certainly favors the patients that got the pembrolizumab arm, which is the top arm across the, up to 18 months. Which for squamous cell, again, really fascinating that these patients are even living that, because that's a much tougher to treat population.

So back to our patient, Mr. Squam. Again, 72-years-old, diabetic metastatic squamous cell carcinoma, and he has no PD-L1 expression. So what treatment recommendation would you suggest for this patient and why?

**Beth Eaby-Sandy:** So, I think it's reasonable to use the triple drug. We certainly would not do a single-agent immunotherapy for someone who's 0%. Would you agree?

**Marianne Davies:** So I would agree with that. And again, I go back to my looking at the burden of disease. I think that that combination really, I wouldn't use a single-agent based on no PD-L1 expression. But that, this patient, in most cases, squamous cell carcinoma has more bulky disease at diagnosis in general, and so I think they need the benefit of both of those.

**Beth Eaby-Sandy:** Would his history of diabetes tell you which taxane? Because this study was done with just taxanes, either paclitaxel or nab-paclitaxel. Your thoughts?

**Marianne Davies:** So we don't really take that into ... I mean, if they're well-controlled diabetic, we don't use that as our driving factor. We would more use just their ability to tolerate the taxane and then it would actually impact our platinum-based agent that we used as far as-

**Beth Eaby-Sandy:** Sometimes the diabetes will come into it because the paclitaxel given at full dose, you're going to give a very hefty dexamethasone dose. As opposed to the weekly nab-paclitaxel, less drug reactions, lower ... Sometimes I even omit the dexamethasone if they have really bad, really brittle diabetes, where even ten milligrams of dexamethasone is just going to put them off the charts for the whole week. So sometimes that can play into it. Though, you know, not every ... Would you do molecular testing in this case?

**Marianne Davies:** In this case, a heavy smoker, squam histology, we're beginning to learn more and more about molecular testing in the squam population. If we had the luxury of time, we would wait for the molecular profile. In our institution, it's reflex testing, as well. So these patients, at first biopsy, it's going to get sent off. So depending on where you are-

**Beth Eaby-Sandy:** Do you reflex squams?

**Marianne Davies:** We do.

**Beth Eaby-Sandy:** You do?

**Marianne Davies:** We do.

**Beth Eaby-Sandy:** We do not.

**Marianne Davies:** Right, at this time we do. It would depend. If it was at an institution, so sometimes people come to you for a second opinion as a tertiary referral center. So if it had not been done, this would not hinder. We would not send the patient for let's say, we wouldn't wait for the molecular profile on a squamous population.

**Beth Eaby-Sandy:** Yeah, and in our institution, we wouldn't even perform it in someone who didn't have a clinical picture. It's just not something that we would routinely do. Right, Beth? I don't think so either. And then what if he has a history of heart transplant, Marianne? What would you give him?

**Marianne Davies:** All right. So great question. So we know that there are some contraindications to the immune checkpoint therapy. And so, we know from much of the data that there is risk of losing your graft with immune checkpoint therapy. Most of the patients that have organ transplants are on immunosuppressant therapy so that they decrease their risk of graft rejection. So, you really need to take that into consideration. The way I would phrase it is that if you have a heart transplant, you really can't afford to lose your heart. You can't afford to have that kind of a toxicity. But if you were a kidney transplant patient, that's a whole different story. Those patients, if it's a risk-benefit, I might take that into consideration. Say, "All right. You know what, there is an alternative. At least you can go onto dialysis if you need to." That provides that type of an alternative. But you really don't have a huge alternative with heart transplants. So we would not, in our institution, at all offer-

**Beth Eaby-Sandy:** My short answer would be, "No way." I think the renal transplant that you bring up is interesting, because in the NCCN guideline toxicity paper, they did do a case series of five patients who were treated with immune checkpoint inhibitor therapy who had renal transplants. And four out of the five rejected their organ.

**Marianne Davies:** But you need to know that. That's your risk-benefit assessment that you're doing if they don't have any other options.

So summary, first-line therapy for non-small cell lung cancer pembrolizumab plus chemotherapy for both squam and nonsquam is now the standard of care by NCCN. Atezolizumab with the bev and chemotherapy is also reasonable in the nonsquam population. There really is no role for nivolumab currently in the first-line setting. They did not meet their primary endpoints in their studies. And platinum-based chemotherapy is really the standard of care. And certainly, you can consider single-agent if a patient does have a high PD-L1 expression.

So now what do we do in the second-line setting? So second-line, NCCN recommends second-line treatment has been docetaxel, ramucirumab, pem in the nonsquamous population if it was not used in the first-line setting, and then the other immune checkpoint inhibitors that we mentioned before, so nivolumab, pembrolizumab, atezolizumab if they were not used in the first-line setting. And I know I always get the question of should we switch over? And there's really not a lot of data right now to support, if you didn't benefit from one or if you benefited for a short period of time, can you try another immune checkpoint therapy. And we're beginning to look at that through a lot of clinical trials now. Or the gemcitabine, also second-line.

And so, just in summary, it's a little bit confusing here, but the CheckMate studies really looking a nivolumab comparing to docetaxel in the second-line setting did show an improvement in overall survival. The KEYNOTE studies at two different dosing also showed improvement with the use of

pembrolizumab over docetaxel and the atezolizumab also. So all three have demonstrated improved overall survival in those patients in the second-line setting over standard of care.

**Beth Eaby-Sandy:** We don't even have to go into PFS, because we're short on time.

**Marianne Davies:** PFS really is the same.

**Beth Eaby-Sandy:** The only thing to note on that was just recently avelumab, it failed to meet its endpoint in the second-line setting.

**Marianne Davies:** So, five year updates continue to demonstrate that these patients had improvement in their overall survival at five years. Again, that magical endpoint that we're just so incredibly interested in. So, what about chemotherapy beyond? These again are questions that we need to continue to answer. So our patient, going back to Mr. Squam, he received nab-paclitaxel, carbo, pem in the first-line setting after 11 months, he developed, on the maintenance pembrolizumab, had disease progression. Good performance status, minimal symptoms. And how would you pursue next line of treatment for this particular patient? So we have, we've listed all the ones that are available for this patient and he's already had front-line immunotherapy.

So the ramucirumab ... Now again, our patient has squamous cell carcinoma, and we know that they're not a candidate to receive bevacizumab, it's contraindicated in squamous. But ramucirumab is another anti angiogenic agent that was explored to see if it would improve overall survival over second-line docetaxel. And again, this was randomized in this patient population. And though subtle, it did demonstrate improvement in the progression free survival in that treat group. So it does add some benefit, although modest. But that might be an option for some of your patients with squamous.

Some of the adverse events we see with ramucirumab are hypertension. So patients need to be monitored for that. And also, a slight increase in neutropenia. So again, those are some of the considerations for that monoclonal-

**Beth Eaby-Sandy:** And importantly, the hemoptysis really wasn't a big issue like we saw with bevacizumab with the ramucirumab. So you can give it to squams, it wasn't much more with the ramucirumab arm than it was on placebos. Actually, it was a slightly less in the squams oddly, so that doesn't seem to be the risk, where we always really worried about that with bevacizumab.

**Marianne Davies:** Exactly. All right. Third-line and beyond. Some clinical pearls, some things to think about.

**Beth Eaby-Sandy:** There was nothing. Clinical trials.

**Marianne Davies:** It's just kind of speculative at this point. Clinical trials, clinical trials, clinical trials. So chemo and immunotherapy really is the standard, certainly, in first-line care now with the consideration for single-agent pembrolizumab. Five year survival has improved, really incredible, as we've mentioned. And then second-line, mostly chemotherapy and immunotherapy if it had not been done in the first-line setting. So we're going to go next to our question.

**Beth Eaby-Sandy:** Let's see our questions again. So a 68-year-old male presents with metastatic non-small cell lung cancer with adenocarcinoma. He's fit, good performance status, he's ready to start first-line treatment. He would like to learn more about which treatment offers the longest survival. Based on this, which treatment would you offer to be best positioned to meet his goal? Pemetrexed, carboplatin, nivolumab? Pemetrexed, carboplatin, pembrolizumab? Taxane, carboplatin, bevacizumab, atezolizumab? Taxane, carboplatin, pembrolizumab? Or you're still unsure.

**Marianne Davies:** He changed up the music. Did you notice that?

**Beth Eaby-Sandy:** Yeah. Okay good. So we had improvement. That is the correct answer. Pemetrexed, carboplatin, and pembrolizumab. There was some vote for the four drug regimen, which isn't wrong. I think because we said, "which would offer you the best position to minimize toxicity and increase survival," we went with that. But I wouldn't 100% say that number three was wrong either.

**Marianne Davies:** Great. All right. We're going to right in to the next. Oh, we've got one more question. Sorry.

**Beth Eaby-Sandy:** The five year survival rate for patients with metastatic non-small cell lung cancer who had a PD-L1 score of 50% or greater and were treated with single-agent first-line pembrolizumab was approximately: 5%, 10%, 20%, 30%, or I'm unsure. Remember I fell off my chair. Good, yeah, so almost 30%, the 29.6% of patients living that long. So yeah, very exciting. Okay.

**Marianne Davies:** Excellent.