SPEAKER: So, I'm going to begin with the first part talking about why we're doing this program and talking a little bit about the field in terms of advance squamous cell carcinoma and why it's an important issue and some other areas that are important related to that. Why are we having this program? Well, one of the reasons is that squamous cell carcinoma is an important disease, and especially when there's metastatic squamous cell or advanced squamous cell, survival drops dramatically with this. Most of the chemotherapy that used, direct straight chemotherapy, is not very effective against metastatic squamous cell of cutaneous nature.

But data for head and neck squamous cells shows there's a potential for PD 1 inhibitors to have an effect on this. We'll talk about this today. The available PD 1 inhibitors are the new one, cemiplimab, we'll be talking about that. And certainly nivo and pembro are out there already. When you think about it, cutaneous squamous cell carcinoma is a very immunologic tumor. It has a lot of immuno targets that can be used to try to treat the tumor and its issues related to immunosuppression.

We're also going to talk about the new data from the cimiplimab to really determine where we are with this. So, here are three types of skin cancer there. You've got a melanoma over on the left. You've got a superficial basal cell pigmented basal cell in the center. And you've got a squamous cell carcinoma on the right. Those are the basic three kinds.

If you look at melanoma, which is the most dangerous, is the least common. But if you look at non-melanoma skin cancer, basal cell and squamous cell, depending how they're counted there's at least three million newly diagnosed cases each year in the US. And if you break down the non-melanoma skin cancer, it's estimated that on the order of magnitude there's about 600,000 newly diagnosed cutaneous squamous cells in the US each year. Now one thing about squamous cell carcinoma, it's in the middle in a bunch of ways.

There's many more basal cells, many fewer melanomas. Melanoma's more dangerous, basal cell is less dangerous. So squamous cell sometimes doesn't get the attention that it really deserves, and like Rodney Dangerfield sometimes doesn't get the respect it deserves either. Some data about squamous cell carcinoma. The rates of squamous cell carcinoma are rising dramatically, cutaneous squamous cell. This is two sets of information in the southern US.

And you could see that among men it's rising, among women rising, not as frequently but it is a significant increase over time with this tumor. The number of cases, again, are not totally accurately counted because you might have the farmer who comes once a year to the GP in Texas who gets a bunch of squamouses scraped off, not even sent into the lab. And they're not officially a reportable disease in many states. But based on that, the most recent estimates is that they're anywhere from 180 to 420,000 annual cases in [INAUDIBLE], and about 5,000 to 12,000 or so cases with [INAUDIBLE], and about 3,200 to 8,700 deaths from cutaneous squamous cell each year in the US.

And why that's important, if you look at the southern part of the US the deaths in cutaneous squamous cell are probably about as common as the deaths we see from renal, oral pharyngeal carcinomas, and even melanoma. So because there's so many more of them, the probability of dying is lower but there's just absolute numbers about the same. The American Academy of Dermatology came out with guidelines of care earlier this year that were published in the JAG talking about the ways to do this. But really the idea of using immunotherapy to treat squamous cells wasn't truly covered there because it's just too new. And we're getting a lot of that new data today.

When we talk about the spectrum of squamous cell carcinoma, obviously there's some early cases, as you see on the left, to advanced cases. And the challenge is to determine which one of these cases are at high risk or risk for metastatic disease and subsequent death. Because it's not easy to necessarily do that clinically. A number of models have been proposed to try to determine what lesions are high risk for disease. This was a paper that was in [INAUDIBLE] *Dermatology* about two years ago, where they looked at significant risk factors for recurrence. And you can see a lot of the things similar you see in melanoma, with thickness, invasion the subcutaneous fat, perineural invasion, diameter, location, poor differentiation, a lot of the things you see with melanoma.

If you look at the risk factors for metastases, again the same theme is there in terms of thickness, diameter, poor differentiation, et cetera. So you see the same thing. And somewhat of the same thing also for disease specific death from cutaneous squamous cell-- diameter, poor location, perineural invasion. So based on these factors, tumor depth is probably really associate with the highest relative risk for local recurrence. And tumor diameter is important with this. We'll show why that's important in a little bit.

But one of the things we don't really have, as I said, is a good data registry, national registry, to collect this data. So some of these are estimates. Scott Bosco put together a model that was published in *Skin* last year looking at this. And they had data from almost 600 patients on 800 or so squamous cells. He did a multivariate regression model to look at this, logistic regression. And it turns out that the factors that were most important were poorly differentiated histology, anatomic location, rapidly growing, recurrent, again perineural invasions.

So some of the same factors that we see with this, the theme again across these models. And this model had a fairly low sensitivity. So no one found one out of 20 or so of the high risk lesions. But it had a very high specificity. So in other words, if it said that you were high risk for metastatic disease in fact you really were at high risk for metastatic disease for this.

Another model that was recently in the *JID* last year was a prospective study analyzing prognostic factors of almost 1,500 cases with a follow up of three years on average. And it turned out that about 3% of the cases experienced tumor specific death. Multivariate analysis showed again thickness, desmoplastic growth, and immunosuppression to be the significant factors with this. Here's another paper that was in *Lancet Oncology* a little longer ago. But again the key factors were thickness, horizontal size, diameter, immunosuppression, near the ears, anatomic site.

So when you put these all together, what you see is kind of interesting. Obviously, diameter appears in all these factors. Thickness appears and depth appears in all these factors. But what are diameter and thickness really a measure on indirectly? And Alexander Breslow found the same thing. Actually depth and diameter are an indirect measure of tumor volume, it's just two of the dimensions.

In fact, when Breslow, he was actually one of my professors years ago when I was a med student, when he looked at this from melanoma he was actually trying to determine tumor volume but just didn't have the tools to do it that time. So thickness was a surrogate for tumor volume and certainly works quite well as an prognostic factor. And similar to what you see in melanoma, you can use this to predict risk in squamous cell carcinoma.

So like melanoma, we've been using these clinical histologic factors to assess prognosis. But with melanoma, we're now using genetics and genomics in diagnosing and melanoma. The question is, can we use the same approach now and in the future to start looking at assessing risk for metastatic disease and death using genetic expression profiles in squamous cell carcinoma? A number of genes have been identified that impact on risk of melanoma-- sorry, of stem cell carcinoma recurrence. These are several of them. The RAS genes appear to be very interesting because they are mutations that definitely have immunological impact and they're seen in about one out of five squamous cell carcinomas, seen much less frequently in melanomas.

So, could you use the same genetic expression profile for this melanoma? And the answer is yes but there's some work to do. So in melanoma, for example, we know there's a clinically unmet need. We want to determine which melanomas act like stage three melanomas, where they're earlier, thinner. In squamous cell we want to be able to identify, obviously, the tumors that are at high risk for metastatic disease. They need to receive adjuvant therapy.

Can you use it to guide management decisions? Well, today the tests used for melanoma are, in fact, being used to guide management decisions. There's a study going on by a company that's developing this test that shows that in fact you will be able to potentially use this for squamous cell. And how could the test be used clinically? Obviously, if you can identify high risk with a simple test that would be quite effective.

You might be able to target the appropriate adjuvant treatment for them for this. This is a series of 18 genes. You don't have to memorize these. But identified that risk for the model and being looked at. And what's interesting with this model is that you have the same roughly sensitivity with this with about the same-- better sensitivity with about the same negative predictive value. So this approach may be quite effective compared to the other clinically based scaling systems.

And the idea behind this, if you use a genetic expression profile test, divide that with the good prognosis and poor prognosis, can that impact on the management of cutaneous squamous cell? Obviously, a test is only good if it makes a difference in management. In melanoma it has. Hopefully in squamous cell it will too.

In terms of therapeutic options, I'm going to only touch on these briefly because we're going to go this a little more depth with the subsequent speakers. We know certainly the new nomenclature of combining PD 1s CTLA-4s into immune checkpoint blockade is important. These are the drugs that are typically thought of for this. And a number of studies have looked at using PD 1 inhibitors are now immune checkpoint blockade drugs for squamous cell carcinoma. I will go through them briefly because we'll touch on them later in the talks.

This was a study of European hospitals looking at this. And in fact, only 17% received systemic antitumor therapy. The treatment was not completed as planned in 50%. But two patients had a complete response, a number with partial response and disease stabilization. So there is potential for this approach.

This is a case study of one patient that had pembro for cutaneous squamous cell. And in fact, this was strongly associated with a positive PD 1 ligand for this. The off label use of pembro has been used in a couple of cases now. We'll be touching on that a little later, too.

This is another case that was done with pembro looking at this. And again, pembro in this case induced complete tumor regression in a patient with unresectable disease. Nivo has also been used again, as a PD 1. And this is a series of three patients that two patients had a partial response who received therapy for greater than 12 months with no adverse effects. What's really exciting and new and we're going to focus on a little bit is a new drug that was just recently approved by the FDA for this, cemiplimab.

And the FDA has first approved this is the first official FDA approved drug. So the other drugs are being used off label for treating cutaneous sqmaous cell. This was actually approved for the use of a advanced cutaneous squamous cell. This was one of the original studies looking at one patient. Again, a series with this had some adverse effects, typically with-- we'll talk about those later. But you do get some from skin effects, other effects with it.

They also expanded from the phase I study, a phase II study. We'll talk about those in a moment. And this is actually the *New England Journal* article that just came out very recently on this. Again, I won't go into this in much detail because our subsequent speakers will be talking about it. But the bottom line in the phase II study, almost half the patients in the study achieved some sort of response, either a complete or partial response. And some have stabilization of disease.

This is a waterfall plot so the lower the bars are the better the patients did. And you see overall you see a significant improvement for the patients in the phase II study. Again, this looks at the time for treatment. And the people who will be touching on this a bit later, our speakers with again showing a response for the phase II study. Again as you see, not everybody responded but about half the patients did. Had patients with progression free survival for over a year for that.

These are just some pictures from that study. And you could see a dramatic improvement for patients who were on the drug for this. There are some adverse effects. We'll talk about those a little bit later, too. But the conclusion was that the new drug, cemiplimab, did induce a response in 50% of the patients with cutaneous squamous cell carcinoma at high risk.

One of the things you do see is granulomus reactions on the skin. We'll talk about that a little later. But again, you can see these things on the skin. As dermatologists, we need to recognize that too.

So these are the references. They'll be in your handout with this.