KARL LEWIS: So my name is Karl Lewis, not the runner Carl Lewis, the medical oncologist Karl Lewis at the University of Colorado in the Cutaneous Oncology program. And, really, our specialty there is cutaneous malignancies. The predominance of what we treat is melanoma. But we do have an active research program in advanced basal cell carcinoma, as well as cutaneous squamous cell carcinoma and Merkel cell carcinoma. And thank you for the invitation to present today.

So advanced non-melanoma skin cancer, this really falls under the category of different tumor types-- squamous cell carcinoma, basal cell carcinoma, Merkel cell carcinoma. And there's really two different groups within this advanced non-melanoma skin cancer setting. There's locally advanced disease, where patients have either one large lesion or multiple smaller lesions that are not easily amenable to resection. And of course, patients who have metastatic disease-- that's either distant metastatic disease, lungs, bones or to regional lymph nodes.

So what is locally advanced non-melanoma skin cancer? Well, this is really poorly defined. And it's an issue when you design clinical trials for these patients to really specifically define what a locally advanced tumor is, because that's important, obviously, in the inclusion/exclusion criteria.

And it's like the Supreme Court said regarding pornography-- I know it when I see it. So you can't really easily define it. But when you see a patient with it, you know it. But in terms of clinical trials, it's defined simply as "not a good candidate for surgery or radiation." So you can see that that leaves open to interpretation what "not a good candidate" is. So there really isn't a specific definition. But you know it when you see it, when these patients come into your office.

These patients really should be presented at a multidisciplinary tumor board, because systemic treatment modalities for these patients really should be on the table. It shouldn't just be local therapy-- surgery, radiation. You should think about systemic therapies, particularly in today's age. And you need to balance the perspective of efficacy-- is this a [INAUDIBLE] intent? Is this palliation? And tolerability of the treatment-- what's the aesthetic outcome of a big surgery, the adverse events of any systemic therapy, and all those things that play a role in terms of the decision making process.

So squamous cell carcinoma, specifically-- a lot of what we go over here is reviewed, already been presented before. But just to go over it briefly, squamous cell carcinoma is the second most frequent non-melanoma skin after basal cell carcinoma. It's about 20% of all cutaneous malignancies. And the incidence rate really is increasing.

It's poorly defined, but that seems to be the trend anywhere you look at the data, a 50% to 200% increase in the last 30 years. The majority of these lesions occur in the head and neck area, chronically sun-damaged locations, which is about 80% to 90% of them. And they usually develop some precursor lesions, actinic keratosis. But they can also develop de novo. And fortunately, more than 90% of the cases have excellent prognosis. So that's the good news.

Here's a picture of somebody with a chronically sun-damaged forehead. I don't like this picture, because that looks like my forehead, growing up in Southern California at the beach. But the progression rate of squamous cell carcinoma is approximately 1 per 1,000 AKs in a five-year follow-up

Post-transplant skin cancer, I think, is an important topic. So these non-melanoma skin cancer incidents are increased in patients who are immunosuppressed, particularly immunosuppressed in the post-transplant setting. And there's a 36-fold higher incidence in organ transplant recipients.

And in the general population, basal cell carcinoma is more common than squamous cell carcinoma. But in the transplant patient population, the squamous cell carcinoma to basal cell carcinoma ratio is about 4 to 1. And these tumors tend to have an aggressive biological behavior. And they do have poor outcomes.

So here's some data looking at post-transplant skin cancer, organ transplant recipients versus the US population. And you can see there is a marked increase. And most of that increase is driven by increases in squamous cell carcinoma. There is an increased risk of melanoma and an increased risk of Merkel cell carcinoma. But squamous cell carcinoma is the predominant issue.

And I think that this is important as it relates to today's topic, because clearly this shows that the immune system played some role in at least surveillance of this tumor. And if you knock the immune system down, the squamous cell carcinomas have the ability to take off. So the immune system clearly plays a role based on the clinical information we gathered here.

So what are the primary treatments of cutaneous squamous cell carcinoma? Well, certainly, it's excision with clear margins and conventional histology.

In terms of staging melanoma, we do sentinel lymph node biopsies routinely. But the value of sentinel lymph node biopsy in squamous cell carcinoma is questionable at this time. There's no clear recommendations in terms of guidelines. At University of Colorado, we do not do sentinel lymph node biopsy as a staging procedure. And so this is an area of active research and an area of debate currently. But the primary treatment is standard excision with clear margins.

But how do you treat locally advanced or metastatic? So if it's not amenable to resection or it has spread to regional lymph nodes or distantly, what are the therapeutic options? Well, historically, there's radiation therapy. It does tend to be a radio-sensitive tumor. So radiation therapy is an option here.

In terms of systemic therapy, cisplatin-based chemotherapy, but there's no established standard regimen. And there's no prospective studies on chemotherapy, that I know of, in terms of squamous cell carcinoma. This was largely derived from data from head and neck tumors. So it was used because we really didn't have something that was better. So there's no standard chemotherapeutic regimen.

And the responses historically tend to be short-lived. And certainly, toxicity is an issue, particularly if patients are elderly, not great candidates for chemotherapy.

Mutation-driven or, really, targeted therapies, so these cancers tend to overexpress epidermal growth factor receptor. And drugs like cetuximab have been used. There was a prospective study out of France that was published in the *Journal of Clinical Oncology* in 2011 that showed using cetuximab had a response rate of about 28%, with about a 70% disease control rate.

A newer monoclonal antibody directed against EGFR, panitumumab showed a similar response rate of 31%, a similar disease control rate of about 70%. And then last year at ASCO, there was a pan-HER inhibitor they looked at. Again, response rates of about 28% and a good disease control rate.

But immunotherapies, is there a role for that? We know in organ transplant recipients, that the type of immunosuppression that they're receiving plays a role in terms of their risk of developing squamous cell carcinomas. So if you can get them off drugs like calcium urine inhibitors and switch immunosuppression towards mTOR inhibitors, that might make a difference in terms of the number of squamous cell carcinomas that they develop.

But then the question that we try to ask, is there a role for PD-1 antibodies in this disease? Here's a patient with what we would consider to have locally advanced squamous cell carcinoma. Whether this is one large lesion or multiple smaller lesions sort of coalescing is hard to say. They were treated with cetuximab therapy. And you can see they had a good response to the therapy. So targeting that EGFR can show benefit. But whether that's long-term is an issue.

And as was just discussed, mutational load likely plays an important role in terms of responding to immunotherapy. And this was shown earlier. This is looking at different tumor types in the mutation burden. And you can see out here at the ends, the tumors like melanoma and lung cancer and bladder cancer, tumors that we know respond to immunotherapy, tend to have higher mutation burdens.

And there was a study that was recently published that looked at an increased number of malignancies, including cutaneous malignancies. And they showed that cancers like basal cell cancer of the skin, squamous cell cancer of the skin, and melanoma really led the way in terms of mutation burdens for tumor types. So this is another clue that cutaneous squamous cell carcinoma may be a good candidate for immunotherapy, because if you believe that the higher the mutational burden, the more neoantigens that are present, the higher likelihood of responding to immunotherapy, this certainly fits the role.

And there were some case reports that have been published that was looked at. Here's a case series out of the University of California San Diego that looked at four patients with cutaneous squamous cell carcinoma and a patient with basal squamous cell carcinoma. And they showed two partial responses. Three of those patients had stable disease. Responses were seen early within the first three months. And the responses tend to be durable, lasting six months or greater. And the drug seemed to be tolerated in this patient population.

Now this was not a prospective study. This was just a case series. And they used both pembrolizumab and nivolumab. So those Pd-1 antibodies have been used in this disease with some success.

And here are some pictures that they published in that paper. And you can see this particularly in the bottom figure here that the patient seemed to derive significant benefit from the use of Pd-1 antibody in this locally advanced setting.

So this paper was published recently in the *New England Journal of Medicine.* And this is looking at a PD-1 antibody, cemiplimab, and advanced cutaneous squamous cell carcinoma. Now here's the baseline characteristics of the patients. And I throw this up for a couple of reasons. One is to go over the two different patient populations. This was a mixture of two different studies. So in the phase I study of cemiplimab. It was an all tumor type, all comers study. They treated a patient with advanced squamous cell carcinoma. And they saw a rapid and what appeared to be a durable response.

So in that phase I study, they did an expansion cohort of cutaneous squamous cell carcinomas. And they enrolled 26 patients in that. Now that was a mixture of different patients. About a third of the patients had distant metastatic disease. About a third of those patients had regional metastatic disease. And about a third of those patients were what would be considered locally advanced. So that patient population is included in this trial.

Then what was done was a phase II study. And in the phase II study, there were two cohorts. There was a metastatic cohort, and there was a locally advanced cohort, metastatic either to the regional lymph nodes or to distant sites. And this paper only includes the metastatic cohort in the phase II study. So the locally advanced data is not mature enough yet. It has not been published. So was published in the *New England Journal* is a mixture of the expansion cohort from the phase 1 and then one of the two cohorts for the phase II.

So patients generally in their 70s, head and neck was the primary location. They were a pretreated population, with a significant number having received previous systemic therapy and about 80% having received previous radiation therapy. And here is a chart of their outcomes.

So if you look at the expansion cohort, those 26 patients, there were no complete responses recorded. But 50% of the patients had a partial response. Only 12% of the patients had progressive disease as their best response. So the overall objective response rate was 50%. And the so-called durable disease control rate was about 65%. And the median observed time to response in that phase I cohort was 2.3 months. So if patients were going to respond, they were likely to respond early.

For the metastatic disease cohort in the phase II study, they saw 4 complete responses and 24 partial responses for an overall response rate of 47%, so very similar to that expansion cohort. And in this situation, 20% of patients, about, had progressive disease as their best response. Again, response is seen early, with the median observed time to response, 1.9 months, in this cohort of patients.

And here's some representative figures from this trial. Here's a guy with a large tumor on his neck. And you can see at week 32, he's had a marked response to therapy. Here's a guy with multiple, surrounding cutaneous lesions on the neck and at week 24, a near-complete resolution of that area. And this picture was shown earlier, a guy with this ulcerated mass behind his ear. And by week 8, he had a marked improvement in that area.

This is a patient from the expansion cohort of the phase I study. And I think this is a really dramatic photo. So this is his baseline, with all these cutaneous metastatic tumor deposits on his scalp. And he's clearly had a large resection in that area in the past, and he's failed. And this is in about six weeks' time he had this response. So you can see these responses rapidly. And here's a side view of that same patient, April 1st versus May 13th, so a dramatic response to the therapy.

And these were both shown earlier. On the top is the so-called waterfall plot. Each of those lines, either up or down, represents an individual patient. And on that waterfall plot, that's the 45 patients in the phase II part of the study that had radiographic assessments. And you can see that the majority of patients had decrease in their tumor burden. There were only a few patients out here that had progression as their best response.

On the bottom figure here, this is the so-called swimmer's plot. Each of these lines is an individual patient. And I put this up because these yellow triangles are the time of partial response. And you can see, of the 28 patients that were responders on this trial, the vast majority of those patients had that response at the time of first assessment. So if you're going to see benefit to the immunotherapy in cutaneous squamous cell carcinoma, it appears that you're going to see it sooner rather than later.

And here's the progression-free survival curves. You can see that Time and Months at the bottom that present who are progression free on the vertical axis. And most of the progression happened early. That curve drops off. And then we start to see-- I've lost my pointer here, sorry-- what we hope is a tail of the curve.

Now the follow-up on this is fairly short. Only a few patients are out past a year. But historically, what we see that has been shown earlier with immunotherapy is that patients who respond can have very durable responses. Their immune system can control the disease long term. And we're starting to see hints of that here with the progression-free survival curve, seeing this so-called tail of the curve here. But we certainly need longer follow-up of this to see that that holds. But we're very optimistic, based on other tumor types, that that will be the case.

Organ transplant patients, as we talked about, is a big problem. Those patients can develop advanced squamous cell carcinomas. And so we need effective therapies for them.

And this is a case report out of Johns Hopkins of a 57-year-old woman who had a renal transplant in 1989. And she was on immunosuppressant with cyclosporin A and steroids, and in 2014, developed metastatic squamous cell carcinoma treated with cetuximab, the monoclonal antibody against epidermal growth factor receptor, and then trametinib, which is a MEK inhibitor, based on the fact that she had loss of function, mutation of a protein called NF1 that drives in that kinase pathway.

And she progressed and felt to be a poor candidate for chemotherapy. So she received off-label pembrolizumab and developed irreversible organ rejection, lost her graft. And they show microscopic evidence that there was PD-L1 expressing immune infiltration consistent with the PD-1 antibody initiating this organ rejection. However, she had an 85% reduction in her metastatic tumor burden. And she continued on pembrolizumab with dialysis.

So immunotherapy does not appear is a very viable treatment for patients who have organ transplants. Certainly, you can lose your kidney and still function. But other transplant patients, like liver transplant or heart transplant, these, we want to be very, very cautious in that setting.

So the conclusions-- cutaneous squamous cell carcinoma generally has a good prognosis. But locally advanced and metastatic disease can develop. And when it does develop, it can be very problematic.

And previously, there's been little in terms of effective systemic therapy options. Chemotherapy, there's little data, and there's significant toxicity. Targeted therapy, there are some clear benefits with drugs like cetuximab. But PD-1 antibodies with cemiplimab in the paper that was published in the *New England Journal of Medicine* was a major step forward. And this was the first drug specifically approved for advanced cutaneous squamous cell carcinoma.

But we still need to improve upon that, because there's the patient populations such as organ transplant recipients. And although the response rate is somewhere around 50% for the PD-1 antibody in this setting, that's not a 100% response rate. So we need to improve with alternative immunotherapies, combination immunotherapies, and so forth.