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## New Systemic Options for Managing cSCC: A Care Team Forum

Narrator:

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Dr. Schmults:

Hello, and welcome to *New Systemic Options for Managing Cutaneous Squamous Cell Carcinoma: A Care Team Forum*. This is the first of a 2-part discussion-based series. I'm Dr. Chrys Schmults, Director of Mohs and Dermatologic Surgery at Brigham and Women's Hospital in Boston and Associate Professor of Dermatology at Harvard Medical School. I'm joined today by my esteemed colleagues Dr.

Omid Hamid, Chief of Translational Research and Immunotherapy and Director of Melanoma Therapeutics and a practicing medical oncologist at the Angeles Clinic and Research Institute in Los Angeles, and Dr. Anokhi Jambusaria, a practicing dermatologist from the Dell Seton Medical Center at the University of Texas. We also have with us 2 honorary guests today: Jim, a patient of mine and a cutaneous squamous cell carcinoma survivor, as well as his wife, Joyce. Welcome.

Dr. Jambusaria, could you give us a bit of an overview of squamous cell carcinoma?

Dr. Jambusaria:

Sure. So, as we know, squamous cell carcinoma is the second most common skin cancer. It's estimated that there are over 1 million cases of squamous cell carcinoma diagnosed annually, and the incidence is rising at about 2% to 4% every year. Surgery is the primary treatment modality for most squamous cell carcinomas. Patients will either be offered a wide local excision or Mohs surgery. And the cure rates are actually pretty good. If you have a nonrecurrent primary squamous cell carcinoma, the cure rate for standard excision is about 92%, and if you do Mohs surgery, it jumps up to 97%. The cure rates are a little bit lower for recurrent tumors. The cure rate for a recurrent tumor with standard excision is about 77%, and it jumps up to 90% to 94% if you do Mohs surgery. And Mohs surgery is really considered to be kind of standard of care for high-risk cutaneous squamous cell carcinoma. It's really reserved for a lot of tumors in areas that are hard to operate, like the head and neck, the genital area, the hands and the feet. It's also kind of what... As dermatologists, we think about referring patients for Mohs surgery if they have a large or aggressive tumor or even a recurrent squamous cell carcinoma, especially since I mentioned the cure rates for standard excision of recurrent tumors is pretty low.

The advantage of Mohs surgery is that it's tissue sparing. It minimizes the amount of normal skin that needs to be excised and so thus giving you the best potential cosmetic outcome, but the most important advantage of Mohs surgery is that it allows for 100% histologic evaluation of the surgical margin, therefore ensuring that the tumor is out prior to reconstruction or closure and thus leading to the highest cure rate. Some of the cons of Mohs surgery is that it's definitely more time consuming than standard excision alone, and you need to go to a specialized Mohs surgeon who is trained to do this particular technique.

Dr. Schmults:

And that evaluation of nearly 100% of the marginal surface, that is particularly helpful in more aggressive tumors?

Dr. Jambusaria:

Yes, absolutely, so more aggressive tumors, especially tumors that might be poorly differentiated or

have single cell spread, being able to look at 100% of the margin to make sure that you don't let some of those little individual cells kind of escape.

Dr. Schmults:

And whether it's done by Mohs surgery or some form of standard excision, that complete marginal surface area assessment is part of current NCCN guidelines for high-risk cutaneous squamous cell carcinoma.

#### Determining Surgical Ineligibility

Dr. Schmults:

Jim, you have had 2 different surgeries for cutaneous squamous cell carcinoma, the first on your face by a head and neck surgeon—and actually, there needed to be a second surgery to completely clear that tumor—and then 2 years later a surgery on your neck. Could you tell us about both of those surgeries?

Jim:

Sure. The first one, the indication—I thought I just had a pimple on my cheek, and when I couldn't take care of it, I went to see my primary care, who referred me to a doctor that removed the pimple on the face and then waited to make sure all the margins were clean. And then I was all set, and I thought I was good to go. Two years later, while shaving, I felt a lump on my neck, and I went back to my primary care, and he recommended that I get some scans done to take a look at it to make sure that something wasn't reoccurring, and unfortunately, it was. It was a reoccurrence of the squamous cell cancer. And then at that point, I went in to Dana-Farber and met with the team, and they recommended a surgical procedure to remove the node, and it was found that it was carcinoma. At that point they recommended... After they removed it, they said that they thought that they got it all. There were a few margins that were a little suspicious, but with some radiation and chemotherapy we could kind of keep an eye on it.

Dr. Schmults:

Jim, do you think that scarring and facial disfigurement are concerns to patients, or do you think that given the much higher cure rate with surgery as compared to systemic therapy, do you think most patients would want to do whatever it took surgically to cure their disease?

Jim:

You just want the disease cured, so I would go with what is the best solution for the problem.

Dr. Schmults:

Dr. Jambusaria, can you tell us a bit about patients who are ineligible for surgery? When is that not an

option?

Dr. Jambusaria:

Sure. So I think that overall, though, most patients—the vast majority of patients are going to be surgery eligible, and for those patients surgery should be discussed because, as I mentioned before, they have really excellent cure rates. I think that there are tumor and patient factors that would make somebody ineligible for surgery. So, for example, if you have an older patient who's unable to tolerate surgery, can't sit or lie down still for 45 minutes to an hour, is unable to take care of their wound, you might not consider surgery for them. There are also tumor factors that are really important, so patients who have very large or deep tumors where surgery is going to involve significant morbidity, so either disfiguring potential or if they have to have a vital organ removed—so, for example, if it's around the eye and they're going to have to have their orbit removed and they're going to lose their vision, that would be something to consider—or if the surgeon, the clinician, has very low confidence that they're going to be able to actually get negative margins during surgery. And then again, if the tumor has spread beyond the primary site, if it's gone to the lymph nodes or other areas of the body, sometimes they are surgically eligible candidates, especially if they have oligometastatic disease, but obviously, if they have multiple areas of involvement—for example, in the case of Jim where he had kind of bilateral involvement—then surgery might not be the primary option.

Dr. Schmults:

Dr. Hamid, have you historically treated patients who are ineligible for surgery?

Dr. Hamid:

Well, in the past we had very limited options. Obviously, the patients that are ineligible with local disease, the discussions about radiation and a radiosensitizing agent were important, and those led to control in a small subset of patients who ultimately would then progress and get grouped into those locally advanced and metastatic patients that required systemic therapy. Unfortunately, those systemic therapies were very inefficacious. What were they? They ranged from chemotherapeutics that worked in other squamous cell carcinomas like squamous cell of the head and neck, and those are the platinum agents, cisplatin, carboplatin, the taxane docetaxel, and also some of the 5FU agents, Xeloda, etc. And those were in some way put into a combination and tried. Again, we also saw, like as is approved in head and neck squamous cell carcinomas, that EGFR was upregulated, so some of those targeted agents like cetuximab were used. Unfortunately, we did not see a huge response rate, nor did we see the fact that those patients that responded benefitted for an extended period of time, what we call progression-free survival.

Jim's Experience with Chemotherapy

Dr. Schmults:

Jim, at what point did your doctors feel that you were going to need something beyond surgery and radiation?

Jim:

It wasn't long after I had the surgery in the neck or the tumor removed, and they felt that they got it all and that everything was pretty good. It was going to be more of a maintenance type thing.

Joyce:

Preventative.

Jim:

Preventative with the radiation and the chemotherapy. It was a week after that that I came in and they could see that it started to metastasize to the other side of my chest, and then it was basically, "Well, that's not going to work. We have to come up with another plan." And at that time, because I was already on the chemotherapy and the immunotherapy or the clinical trial was suggested, I wanted to go to the immunotherapy. I just, again, was afraid of chemotherapy, the side effects of it. I opted to go on the clinical trial at that point.

Joyce:

We were excited at the opportunity that a clinical trial was available, because again, we didn't hear really positive things about if he had to go on chemotherapy for the long term. It would be like we're going to buy some time, but we weren't going to really see any real progress, so that's how it felt.

Dr. Schmults:

And you were getting radiation concurrent with cisplatin chemotherapy, weekly cisplatin, but I think you only got a couple of treatments before it was clear that that just wasn't working.

Jim:

It was right in the beginning, yeah. I believe I had 1 treatment of radiation and—I'm sorry, of chemotherapy—and then maybe 2 of the radiation, but then the other tumors started to be seen on the other side of the chest, and that's when they performed a biopsy and they said, "Okay, this doesn't look like it's going to work. We can up the amount of or change the chemotherapy, amount of it, but we also..." What I was saying, at the point they said, "But we also now have a clinical trial if you'd be interested in it," and that's when I opted to do the clinical trial. I didn't want to get on the road of just increasing chemotherapy. And again, just the fear of... You know, I'm not a doctor. I'm a street guy. You just hear the stories of chemotherapy and people losing their hair and neuropathy, and I just didn't want to go that route not even knowing the results of the clinical trial, but to me, I was willing to go that route,

so I gave that a shot. Thank God I did do it, yeah.

### **PD-1 and L1 Inhibition**

Dr. Schmults:

Dr. Hamid, why were PD-1 drugs thought to be potentially particularly beneficial for cutaneous squamous cell carcinoma?

Dr. Hamid:

Well, that pathway works in our bodies normally to prevent a huge immune flare. So we've known about the pathway for a significant amount of time. If we didn't have it, there would be an increase in autoimmune complications. But we had seen that by targeting this pathway, that we could see responses in other solid tumors. So the PD-1/PD-L1 pathway works as an interaction between the T-cell and the tumor. The tumor has co-opted this pathway and increases PD-L1, and the T-cell has PD-1 on it. Those 2 things dock together, and that causes the T-cell to become ineffective. It dampens the immune response. Normal tissues use it to protect themselves from immune action. Tumors have just taken that and increased it on their surface, and that allows them to remain sort of cloaked to the immune system. We have seen in multiple solid tumors that by making antibodies, these antibodies come and block PD-1 or PD-L1 and doesn't allow these 2 things to dock together. We can reinvigorate the immune system and allow it to attack the tumors and to control tumor.

Dr. Schmults:

So, in talking about PD-1 drugs, we now have cemiplimab, which is the first FDA-approved drug for cutaneous squamous cell carcinoma that's locally advanced or metastatic and unlikely to be cured by surgery and/or radiation, and this is our first FDA-approved drug for this disease. We've waited a long time to have an FDA-approved drug for the disease, because the prior treatments, that only had maybe a 20% response rate and not a very durable response rate. Most patients who did respond would pretty rapidly relapse after an initial 6 months or so response period. The drug was brought to market with only about 85 patients in the trial, but because there hadn't been... Because this is actually a pretty small subset of a very large cancer—cutaneous squamous cell cancer affects almost 1 million people a year—this subset that develops advanced disease, aggressive disease, is really small, and so you're not going to have hundreds or thousands of patients enrolled in a trial like this.

The cemiplimab trial was not a randomized study. There was just a single arm of just patients treated with cemiplimab monotherapy, and this was thought to be all right because of the failure rates being quite high with systemic therapies that had been tried to date and the lack of a clear established care standard in this disease. The population was very predominantly male in this study. And this is another interesting thing about cutaneous squamous cell carcinoma. The disease itself, and then particularly

the aggressive high-risk subset of the disease, disproportionately affects men, and about 80% we estimate of the people who die from it are men, and in the cemiplimab trial this was reflected in that about 90% of the study cohort were men. Most of the patients had had radiation prior to enrolling in the trial, but only about 30% to 40% had had a systemic therapy prior to enrollment, and this again is likely because of the poor efficacy that we've seen with other systemic agents. And so, as soon as the trial became available, patients who we could see were failing with with surgery and radiation, we really wanted them to be able to be put into this trial as a first-line therapy. Because there is no established first-line therapy for systemic therapy prior to this, we didn't feel that patients had to fail some other standard therapy before being eligible to enroll in the trial.

Dr. Hamid, would you consider a 50% overall response rate as a good response rate in this particular population?

Dr. Hamid:

I would, absolutely, given the lack of other therapies having similar response rates and the durability of these responses. If you look at the Migden paper in the New England Journal of Medicine, you can see that these patients who responded initially had, just like Jim has said, a rapid response, so you can start to see benefit, and that translates into palliation. Not only was it a rapid response, but it was a deep response, which means that the amount of tumor that was affected was significant. And when you look at these Bider (phonetic)\*16:27 plots, the duration of response is still ongoing in a significant population. Also, when you talk about response rates, you're not discussing those patients who had a stoppage of growth and some minor shrinkage, and that population in this tumor was significant.

When you look at the responders, there were a few people who responded who ultimately began to have tumor growth. The majority of those people who responded are continuing to have a response, and that is a wonderful indication about the durability of a treatment like this. And there are patients who have had 100% response, which means every known evidence of tumor is gone, whether it be on skin exam, on CAT scanning or MRI, and when you translate that into our experiences with immunotherapy for other solid tumors, you can see that those patients are the patients where the tumor never comes back.

Dr. Schmults:

Absolutely. We'd certainly like to be able to...

Joyce:

That's exciting for us, you know, to hear such positive response long term.

Dr. Schmults:



Yeah.

Dr. Hamid:  
Absolutely.

Dr. Schmults:

We'd love to be able to push beyond that 50% response rate, but the point that you made about how there are also people beyond that 50% who have disease stabilization, that's important as well.  
Immunotherapy, Efficacy

Dr. Schmults:

Dr. Hamid, could you give us your thoughts on this Kaplan-Meier curve here showing progression-free survival from the cemiplimab trial?

Dr. Hamid:

Right. Dr. Schmults, this is exactly what we want to see to instill confidence in this therapy and how it affects our patients. What we're really seeing here is that there are some patients who have their tumor ultimately grow, but as you get out and you see past a year, there is a plateau of that curve. We still haven't hit where 50% of patients have failed to have benefit after initial benefit, but the plateau shows that you're going to see people having a durable response for an extended period of time, and this translates into overall survival. And what I expect to see here is what we've seen with immunotherapies in other solid tumors, that ultimately, when you look at these survival curves, you will have a subset, a proportion of patients, who will be cured, who will have long-term survival benefit from this therapy for years and beyond, and that's not what we saw with our other therapies for locally advanced and metastatic disease. Ultimately, all those patients had tumor growth, tumor progression, and here, this is giving us the confidence to tell our long-term patients that you're going to really do well. And that's exactly what we want for Jim and Joyce, to be able to sit down ultimately and say that this risk you took on the therapy is going to pay off for you and for other patients, other people like you, sitting in the same chair.

Joyce:

I think it already has. I think we've already seen it.

Dr. Hamid:

And it already has.

Joyce:

Yeah.



Dr. Schmults:

Dr. Jambusaria, how do you anticipate the approval of cemiplimab changing your practice as a dermatologist?

Dr. Jambusaria:

You know, I think that it's been really kind of a huge game changer in terms of how I think about my patients who I diagnose with metastatic disease. Previously to this, they had very few options—and which we've discussed some of them are not very good options—and so we were usually telling them you could consider surgery if you're a surgical candidate, and if not, then you would have to basically jump to some type of systemic therapy. Now I can go to these patients and say that I have a good option for you where you can do pretty well and you have a very good progression-free survival, as was outlined. And so I think that it's just another medication in our armamentarium that we can kind of talk to patients about and basically give them hope that there is kind of light at the end of the tunnel.

Dr. Schmults:

Dr. Hamid, how about you as a medical oncologist? How is this changing how you approach this patient population?

Dr. Hamid:

So, for me, I want to see the patients at any time during their diagnosis. In the metastatic and locally advanced setting, absolutely I'm reaching out to dermatologists and radiation oncologists and relating this data. But we are going to be working on some adjuvant trials for high-risk patients to decrease the risk of relapse, so what we're seeing here for me is a paradigm that for all patients with cutaneous squamous cell carcinoma, medical oncologists are becoming involved in assessing risk and treatment.

Dr. Schmults:

I think, for myself as a dermatologic surgeon and Mohs surgeon, it does start to beg questions about where you draw that line to deem somebody surgically unresectable, and weighing in patient factors, patient comorbidities, their reconstructive challenges after surgery, we can weigh those things a little bit differently now that we do have a systemic therapy with efficacy, but we still have to bear in mind that it's about a 50/50 shot, and particularly for sustained remission. Surgery still has that higher cure rate, but we're anxiously awaiting the adjuvant trials, as you mentioned. I think neoadjuvant could play an important role, particularly with really disfiguring surgeries, high-morbidity surgeries like loss of an ear, loss of an eye, so we're looking forward to those kind of studies to broaden how we can use this medication.

### **Pseudo-progression**

Dr. Schmults:

Jim, you participated in the clinical trial for cemiplimab. Can you tell us about your experience?

Jim:

Yeah. Basically, it was a process I came in every other week for an infusion. It wasn't painful. It took half hour, 45 minutes. People were extremely nice. I could see the progress pretty early in the whole process. And compared to the other options that were originally given me, this clearly was the best way to go.

Joyce:

We spent like so much time being excited about how easy the process was. I mean, you know, we'd come home, Jim would maybe lay down for half an hour just because he felt like he should, but we'd be out to dinner that night. I mean, the side effects were negligible.

Jim:

They were. Yeah, yeah.

Joyce:

I mean, it was really... It was amazing.

Jim:

And like I said before, if somebody wasn't telling me I was sick, I really didn't know that I was sick. I mean, it was such an easy process. I mean, it really, really was and, you know...

Dr. Schmults:

That's fantastic.

Jim:

It is. It was fantastic.

Dr. Schmults:

And how did you feel about how things were explained to you in this study? Were there any unexpected things that...

Jim:

No. No, actually, right in the beginning, worst case they said, "Things might even get a little bit worse before they get better, but don't worry about that because that happens," and to tell you the truth, I think I only heard that once or twice, that one of the tumors looks like it's getting a little bit bigger but don't worry about it. And then by the time I came back for my next scan or treatment, it had either shrunk or, you know, had minimized it. You know, it got smaller again. So, all along, everything I was

told was right on. I mean, there was no all of a sudden, “Well, we weren’t expecting that.” Everything was pretty well, pretty well explained and understood, I think, even at my level. It wasn’t too complicated.

Joyce:

Again, we were coming from the point before we started the trial when the lesions were just like a forest fire. I mean, it was almost daily I could see the advancement of the disease. And one of the oncologists at Dana-Farber said to us, “I know you can’t picture this improving, but it can. You just have to trust it.” That’s exactly how it was. It was almost like they just melted away. It was a phenomenal thing to experience, really.

Dr. Schmults:

I’m glad you didn’t have to go through the experience of having to get worse before it got better.

Joyce:

No, we didn’t.

Jim:

No, no, not at all. Like I said, just the initial when I stopped the chemo and then for not being able to do anything for 30 days or whatever...

Dr. Schmults:

You could see it getting worse.

Joyce:

That was the worst part.

Jim:

There was even a time I was contemplating like, geez, maybe, maybe I should, you know, just get back on the chemo rather than wait this out, because that’s how bad it was getting; but again, I’m glad I didn’t. I’m glad I didn’t, you know, so...

Dr. Schmults:

Yeah, yeah, that’s an important point. That time getting to therapy can really matter in this disease, I think.

Jim:

Yeah.

Dr. Schmults:

The “getting worse before it gets better” refers to pseudo-progression, which is an entity where inflammatory cells will be drawn into the tumor and you’ll see it getting bigger, which in cutaneous squamous cell where patients can physically see it can be disconcerting. Fortunately, it’s fairly rare. It’s only about 5% of patients that get that pseudo-progression, and it does turn around quickly. And most patients who are going to respond, you start to see that response within 2 or 3 months, so you can tell pretty quickly if it’s working well for somebody.

Jim:  
Yeah, yeah.

### **Immunotherapy, Safety**

Dr. Schmults:

Dr. Jambusaria, what are some of the safety concerns that you think about when you’re thinking of cemiplimab for a patient?

Dr. Jambusaria:

Absolutely. So, you know, this is a... As a PD-1 inhibitor, cemiplimab, like other PD-1 inhibitors, activates your own immune system to kill off the cancer, and so most of the side effects are kind of immune-mediated side effects. In the clinical trial, all patients had some type of side effect associated with administration of the medication. However, only about a third of them really had a severe side effect, and less than 10% of them needed to discontinue their medication during the period of clinical trial. The most common side effects were diarrhea, fatigue, nausea, constipation, more GI side effects. There were also some skin side effects where people can get different kinds of rashes, as well as some lung inflammation, some pneumonitis. However, in the majority of these patients, they were very mild and generally well tolerated. Very few patients had Grade 3 side effects or higher.

Dr. Schmults:

Dr. Hamid, would you like to add anything to that?

Dr. Hamid:

So, with these class of agents, when you look at the Grade 3 or 4, those severe side effects, the majority were lab associated and asymptomatic for patients. It’s important for us to relate these side effects and how they can present to patients, because if you catch them early, they can be very reversible and really don’t have an effect for the patient. When you look at the incidence of these side effects and how many of them were significant, you can see it’s much less than you would expect with chemotherapy and really, as Jim has said, did not impact life, lifestyle, daily events.

Dr. Schmults:

We had 2 patients in their mid 90s enrolled at our site at Dana-Farber, and both of those patients tolerated the drug very, very well. Because our patient population in this disease can be quite elderly, quite frail, that's so helpful as compared to, say, platinum-based regimens, which we were using previously, where you really wouldn't dare put people in that age group on those drugs for the most part.

I think that the 10% dropout rate, discontinuation rate, in the trial that you mentioned is important, especially in comparison to basal cell trials with hedgehog inhibitor drugs where about 30% to 40% of those patients had to drop out of the trial due to intolerable side effects, so this drug is much better tolerated than that class of medications.

### **Immune-related Adverse Events**

Dr. Schmults:

We'd like to refer our audience to the manuscript that was published in JCO over the summer of 2018 that outlines the NCCN and AJCC guidelines for managing adverse events from immunotherapy. And as you both mentioned, it does show that for Grade 1 side effects, most of these can be managed on an outpatient basis with oral prednisone. Grades 2 and 3, depending on the severity and the context, sometimes need inpatient hospitalization or high-dose steroids. And it's really only the Grade 4 side effects where treatment might have to be permanently discontinued. A lot of patients either need a drug holiday while they're undergoing treatment, or for Grade 1 side effects can continue right along with their therapy while they're being ... with prednisone. But please do refer to those guidelines for an in-depth discussion.

That's it for today. Thank you for participating in this Care Team Forum. Please don't forget to take the posttest and complete the evaluation to receive CME credit, and stay tuned for part 2 of this series where the panel and I will discuss how to select the right patient with cutaneous squamous cell carcinoma for immunotherapy. Thanks again.

Narrator:

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